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BACTERIOPHAGE WITH SPECIAL REFERENCE TO PLAGUE AND CHOLERA.

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The bacteriophage question is one of comparatively recent date. It may be said to have been definitely promulgated by TWORT (1915) in his "Investigations on the Nature of Ultramicroscopic Viruses," with his discovery and discussion of the glassy or watery colonies of staphylococci which appeared on nutrient agar plates sown with glycerinated calf vaccinia. The protagonist of the bacteriophage theory is, however, undoubtedly D'HERELLE, who has been its ablest exponent and the focus of attack for some sixteen years. The theory of the "bacteriophage," that is of a minute, ultramicroscopic, living organism, parasitic upon and lytic towards bacteria, was given out in 1917. It has undergone surprisingly little change since that date, in spite of the fact that it has been fundamentally opposed. As in all arresting discoveries there are to be found indications of conscious or unconscious appreciation of this phenomenon by previous workers. HANKIN (1896) drew attention to the bactericidal action of the water of the Ganges and of the Jumna for the cholera organism and, according to D'HERELLE, he was probably face to face with the phenomenon of bacteriophagy. GILDEMEISTER (1917) observed and remarked upon peculiarities of texture and architecture in colonies of intestinal organisms. He figured nibbled, defective colonies of dysentery and coli (Flatterformen), which are undoubtedly exhibitions of the bacteriophage phenomenon in the specially sensitive typho-coli group. As, in this controversy regarding bacteriophagy, D'HERELLE practically holds the stage from the commencement with abundance of clear, forceful exposition, it may be well in a review such as this to make his work the main source of reference in discussion. Two of his works are: "The Bacteriophage," (1922) and "The Bacteriophage and its Clinical Applications," (1930). Of these two, the latter has been mainly used as authority for the statements made in this survey. Although this

review has special reference to cholera and plague, it is apparent that the subject requires for its adequate presentation and understanding a much wider basis than is afforded by these two diseases. In consideration of the fact, however, that most of the evidence points to the close association of bacteriophage with organisms of the gastro-intestinal tract, it is simple and justifiable for the reader to make substitution of the intestinal organism *V. cholerae* for such organisms as *Bact. coli*, *Bact. typhosum*, *Bact. dysenteriae*, etc., when these latter are used for illustration of the properties of the bacteriophage. As the organism of plague, *Past. pestis*, is not an intestinal organism it is placed in a somewhat different, but none the less interesting, category from the cholera organism. D'HERELLE evidently regards this organism as having little in common with either the enteric or pyogenic groups of bacteria.

Nature of the Bacteriophage or Lytic Principle.

The controversy over the nature of the bacteriophage is by no means settled. In fact it is essentially a controversy over the nature of life. There is perhaps little likelihood of a revival of the disputation upon the possibilities of spontaneous generation of living from non-living matter, the archebiosis and heterogenesis of BASTIAN (1874). That was regarded as having been settled by PASTEUR'S (1862) experiments on the vital theory of fermentation, which established the doctrine, *omne vivum ex vivo*. "The progress of science," says PASTEUR, "shows more and more that the study of actions brought about under the influence of vegetable or animal life however complicated leads back ultimately to the discovery of phenomena which belong to the cell." Had the demonstration, however, of the existence of ultramicroscopic viruses and especially of an ultravirus such as the bacteriophage, having dimensions (20–30 μμ*) of the same order as those of a molecule of serum-globulin (d'HERELLE, 1925a) or very close to that of a particle of collargol (PRAUSNITZ, 1922) been made earlier, we may wonder whether this controversy would have died down as completely as it has done. The size of bacteriophage has been determined by testing the limits of filtration through graded collodion membranes. The recent studies of ELFORD and ANDREWES (1932) show that phages are composed of particles "whose size is uniform for any one phage" though varying from phage to phage. The estimated diameter of the smallest phage was 8–12 μμ and that of the largest probably between 50 and 75 μμ. The phage, according to D'HERELLE, "in view of its size . . . can only be formed of a simple protoplasmic micella. This, in itself, suffices to demonstrate that the cellular theory of life is false ; that the cell is not the unit of life." This again is a blow at the equally famous doctrine of VIRCHOW (1858) that "a cell can only develop where a cell has preceded it," a doctrine which was first promulgated by GOODSIR (TURNER, 1868, p. 92) in 1845 (MCKENDRICK, 1888, p. 203) and has been expressed in the phrase *omnis cellula e cellula*. A micella, it may be explained, is the term used for an aggregate of molecules, ions, or both, in a colloidal solution. The ultramicroscopic virus according to TWORT may well belong to a "field of life more lowly organised than the bacterium or amoeba" (*loc. cit.*) or may be, in D'HERELLE'S phraseology, a protobacterium. DALE (1932) speaks of the ultramicroscopic viruses as "almost on the border line between unorganized

* 1 μμ, or millimicron, = 1–1000th μ, or 1–1,000,000 mm.

toxic principles and organized living beings." GYE and LEDINGHAM (1930) make the remark with regard to theories denying the living character of viruses :—" The suggestion put forward by SANFELICE in 1914 that a virus is a non-living poison elaborated by affected cells and possessing the power to affect new cells, provoking in them the formation of a further quantity of the poison, forms the basis of most rival theories."

What we have so briefly said will suffice to indicate something of the nature of the implications which are bound up in bacteriophage theory, or, in a wider sense, with the subject of the ultramicroscopic viruses generally. According to D'HERELLE (1927) two main hypotheses exist :—as to its physical nature, whether it be in solution or in suspension, and as to its biological nature whether " it is derived from the bacterium itself and in that case is an enzyme, or it is independent of the bacterium and so can only be a living autonomous being which utilizes bacterial substance in order to reproduce. No other hypothesis is logically possible." We may decide at the outset to adhere, purely as a working hypothesis, to the first of the two alternatives enunciated by D'HERELLE.

Bacteriophage is particulate in character, as seems to be apparent from the way in which the phenomenon of bacteriophagy can be made to distribute itself in the shape of areas of clearance of growth or " colonies," quantitatively and discretely over the surface of an agar plate sown with a susceptible bacterium. By its transmissibility in indefinitely continuous series in cultures of young growing bacteria and its multiplication bacteriophage behaves like a living organism. But these characters, as applied to an invisible object, may not be absolutely convincing and for those who are not convinced it will be convenient simply to replace the term " bacteriophage " by that which is also frequently used, " lytic principle." D'HERELLE describes the bacteriophage as an autonomous, living, strictly parasitic organism belonging to the group of filterable viruses, which multiplies at the expense of, and causes the dissolution of, bacteria. He restricts its character further by maintaining that " there is but one bacteriophage, but as isolated from the organism there is an infinite number of strains." To this parasite he has given the name *Protobios bacteriophagus*.

The main dissentient theories may be summarized as :—the theory of KABESHIMA (1920) of production of a defensive secretion by the intestinal glands acting as a catalysator on the proferment contained in all bacteria to cause their digestion ; the bacterial disintegration or living filterable, fragment (" Splitter ") theory of BAIL (1921a) with its later addition of derivation from chromosomes (1923) ; perhaps most important of all, either in its first form or in its modifications, the theory of an inherited though originally acquired autolytic power by bacteria of BORDET and CIUCA (1921) ; the gene theory of WOLLMAN (1920, 1927) based on DARWIN'S " pangene " theory of transmission of acquired characters and on BORDET and CIUCA'S theory of hereditary transmission of an acquired power of autolysis by the bacterium ; the theory of HADLEY (1927, 1928) in which the bacteriophage is " either a definite stage in the cyclogeny of the bacterial species, or a functionally active particle accessory to one of these stages " ; and the theory of ferment-like action of colloidal particles of bacterial cytoplasm of OTTO & MUNTER (1924). These various theories are of two types : (1) the agent is a living ferment ; (2) the agent is a non-living ferment.

Bacteriophagy. Transmissible Bacterial Lysis.

Early attempts to isolate a bacteriophage for the *Vibrio cholerae* were not very successful. This was attributed to the high mortality of cholera and the difficulty of getting convalescents at the right stage to supply a satisfactory phage from the faeces. The phenomenon of bacteriophagy was worked out and demonstrated, in the first instance, almost entirely with organisms other than those of cholera and plague. In recent years, however, the phage for cholera, and to a less extent that for plague, have been much studied in British India. The typical experiment to illustrate the isolation of a phage and the production of bacterial lysis, as it applies to the *Vibrio cholerae*, may be given in D'HERELLE's own words: "Let us take the stool of a patient recovering from . . . cholera, emulsify a fragment of this stool in water and then filter the suspension through a porcelain filter. . . . The clear, filtered fluid contains a principle which has the property of destroying and dissolving *in vitro* cultures of the specific bacterium responsible for the disease present in the patient. If, for example, we introduce a trace of the filtered stool of a cholera convalescent into a fairly turbid culture of the cholera vibrio this culture will become perfectly clear after two or three hours; all of the vibrios will have become dissolved. . . . If, then, we introduce a trace of this limpid liquid into a second turbid culture of the vibrio the same phenomenon of dissolution takes place . . . and this operation can be repeated indefinitely without the phenomenon of dissolution exhibiting any reduction in rapidity or intensity." In this experiment there are exhibited the most important characters of the bacteriophage-lysis of a bacterium, filterability, and transmissibility or subculture in series with living and growing bacteria. One of the main characters of the phage is that it requires for its propagation the presence of living organisms and it agrees in this respect with the filterable viruses which can only be grown in the presence of living cells. The high degree of activity of a potent phage can be demonstrated by means of the same type of experimentation but with a dilution of the original stool filtrate to as much as 1 in 1,000,000 or more. A bacteriophage, which is isolated from the stool of a cholera convalescent, will usually act most upon the *Vibrio cholerae* itself, although it may also exercise a weaker action upon related vibrios. Specificity of action with regard to a single organism is not, however, an invariable rule with bacteriophages and some may be active towards entirely unrelated species of bacteria. Thus, for example, CIUCA (1923), who does not consider the cholera vibrio to be capable of acquiring what, with BORDET, he calls transmissible vitiation of nutrition, found in the stools of five cholera cases, four of which recovered, a phage which was active not to the cholera vibrio but to *Bact. coli* and *Bact. dysenteriae*. In these cases presumably the phage was simply the common intestinal phage. The same applies probably to the anti-plague phage found in canal water by FLU (1927) which dissolved both *Bact. coli* and *Bact. dysenteriae* (Shiga). D'HERELLE has altogether opposed the conception of different species of bacteriophage, whether they have a restricted action towards one bacterium or a wider range. TOPLEY and WILSON (1929) consider that he has burdened his theory unnecessarily by thus asserting the unity of his phage viruses.

Plague is not an intestinal disease but D'HERELLE apparently believes that its phage is primarily elaborated in the intestine. Its appearance in other situations and other fluids may be due to passage

from the intestine, to contamination with faecal matter, to transport by macrophages or to entry into the circulation. His first name for this organism was *Bacteriophagum intestinale.* The experiments and the views of BORDET and CIUCA (1920 a, b) are perhaps the most widely quoted in opposition to those of D'HERELLE. In their experimentation BORDET and CIUCA filtered the leucocytic exudate which occurred after 3 or 4 intraperitoneal injections of *Bact. coli* at intervals of a few days and found this to be lytic. It is interesting therefore to find that MEISSNER (1924) beginning with intraperitoneal inoculation of *V. cholerae* and cholera serum, obtained a cholera phage from the exudate, but that a proportion of her guineapigs also yielded a lysin from exudate obtained by injection of simple nutrient bouillon. She found, moreover, that the guineapigs which did not yield a lysin with bouillon also failed to yield any lysin after inoculation with cholera-serum mixture. In barbone, which is a pasteurella disease—the plague or haemorrhagic septicaemia of water buffaloes—it was from the faeces of the recovered animal that D'HERELLE (1921) isolated bacteriophage. The field of action then of the intestinal bacteriophage is not entirely restricted to the intestine. " It is capable of passing into the circulation and of inducing bacteriophagy in the fluids and in the organs " and again : " In a disease such as bubonic plague dissolution of cultures of the plague bacillus can be induced by material derived from a bubo of a plague convalescent." That phage is not more frequently found outside the intestine was explained by D'HERELLE (1922) as due to its phagocytosis and destruction by leucocytes (BRUYNOGHE and MAISIN, 1922). This fact is also used to negative the idea that phage can be of leucocytic origin. The existence of plague phage outside the intestine has been shown by ADVIER (1932 a and b) in blood and by PONS and DURIEUX (1932) in bubo fluid.

Although the phenomenon of bacteriophagy has here been first described in its classical experimental form of the action of a stool filtrate upon a young bouillon culture of cholera vibrios, this is probably not the most important method of demonstration. When such a young culture is inoculated very lightly with its bacteriophage, plate cultures made from this suspension on nutrient agar and the plates incubated, it will be found that, if all the conditions required have been fulfilled (appropriate potency of phage, appropriate dilution of the phage and sensitivity of the vibrios), there will be seen upon the surface growth which takes place a certain number of more or less circular areas generally called plaques, within which no growth has taken place. These are the so-called colonies of bacteriophage. They may vary in size from that of a pin head up to 4–5 mm. Clearance of growth occurs where the cholera vibrios have been dissolved. This mode of demonstration of phage is most important for two reasons. It affords in the first place one of the chief arguments for the particulate nature of the bacteriophage. If the addition of phage has been very light the plaques will be discrete, if massive they will be confluent and if massive and highly potent there may be no growth at all, for the organisms will all have been killed and dissolved by the bacteriophage. " Size of a phage," say ELFORD and ANDREWES (1932), " is an important factor in controlling the size of plaque produced. Small phages tend to give rise to large plaques on agar and conversely." By means of dilution of phage and the procural of discrete plaques it is, in the second place, possible to elaborate a method of estimating the concentration of phage in exactly the same way as is done for bacterial

suspensions. Now if the plates with their areas of clearance or plaques are still further incubated it is found that after a certain time small colonies develop in these clearance areas. The same happens with the bouillon culture which has first been rendered limpid: it becomes turbid again. Here we have evidence of the development of secondary colonies or culture composed of a strain of cholera organisms which is resistant to the action of the phage, a lyso-resistant strain of vibrio.

Strains of any bacterium, say the cholera vibrio or the plague bacillus, are divisible, from the phage point of view, into lyso-sensitive and lyso-resistant. Lyso-resistant organisms are again sub-divided into lysogenic and non-lysogenic. A lysogenic organism is one which is accompanied by its phage. It must necessarily be resistant, for it could not exist and yet lead to the production of the specific lytic principle or bacteriophage. The colony, which contains lysogenic organisms, will on plating out yield colonies of all three kinds, that is the lyso-sensitive and the two varieties of the resistant organism the lysogenic and non-lysogenic. With successive transplants in liquid media it is found that, ultimately, transfer to agar will furnish only lysogenic organisms. A lysogenic organism may, however, still be sensitive to a phage from some other source. The explanation of lysogenic strains will vary according to the bacteriophage theory which is favoured. They are, according to BURNET (1930), " most frequent in the least specialized forms " of bacteria, as is also relative resistance to phage. According to him the most reasonable way to co-ordinate the facts is to believe that lysogenesis and associated resistance form part of the physiological make-up of the more primitive bacilli. D'HERELLE, on the other hand, explains this character of bacterial lysogenesis as an example of symbiosis between bacteriophage and bacterium. Such symbiosis he regards as " extremely frequent in nature." Among 18 strains of *V. cholerae* tested, NOBECHI (1926 a) found 6 resistant and non-lysogenic, 9 sensitive and non-lysogenic and 3 resistant and lysogenic. The symbiosis between bacterium and phage is in some respects analogous to that between bacterium and host observed in chronic carriers. The cholera vibrio when it is the subject of symbiotic association is not necessarily manifestly lysogenic (ASHESHOV, 1932, p. 141): it is not till such a bacterium is itself lysed that this phage is liberated into the ambient fluid and appears in a filtrate.

Lytic action, then, on sensitive bacteria is the main distinctive characteristic of a bacteriophage. This action may be watched under the microscope and consists of swelling and spherulation of the affected organism, development of granularity and finally a disintegration, which may take place rather suddenly. Phage is even supposed to have a positive chemotaxis for susceptible bacteria. D'HERELLE himself however, seems to reject the view of positive tropisms in his remarks with regard to the enterotropism claimed for the cholera vibrio. The attack of phage upon the bacterium has been compared to that of a malarial parasite upon an erythrocyte with rupture of the latter and liberation of the proliferated parasite. Secondary colonies, as has been explained, arise in the plaques produced by phage action. Besides being resistant to lysis these colonies, and the organisms of which they are composed, may exhibit highly important differential characters such as mucoid growth and alteration of agglutinability, of antigenic action and of virulence, characters indeed which, in the main, distinguish the " rough " variant from the normal or " smooth " variant of a bacterium. The subject belongs properly to that called " dissociation,"

but is considered to some extent later in its relation to mutation of the cholera vibrio and the plague bacillus.

Filtration of a lysed growth has given a filtrate from which, according to some workers, a growth of the lysed organism has been obtained. If this be so, it would signify the existence of filterable forms (ultraforms) in the life cycle of the bacteria. The fact itself, however, is contested, among others by BRONFENBRENNER and MUCKENFUSS (1927) and is ascribed by them to failure of the filters or technique. The subject is a very important one. For cholera these are " proto-vibrios," which then develop into the ordinary bacterial forms.

Some phage experiments may be fallacious for the reason that it has not been realized that the strain of organism used is itself lysogenic. Thus the phenomenon of bacteriophagy is full of pitfalls for the unwary investigator. Mention may be made in this connexion of the ubiquitous occurrence of the bacteriophage, or perhaps one might say the ubiquitous occurrence of faecal contaminations, as a source of fallacy in experimentation. Contamination is much more difficult to avoid in dealing with phage than in dealing with bacteria.

The source of phage is according to D'HERELLE the intestine. It does not make its first appearance during a disease, for it is already present in the intestinal contents and is continually developing at the expense of the common *Bact. coli*. Thus it is already apparent in the intestinal contents 7 to 8 days after birth. The bacteriophage, which by growth *in vitro* or *in vivo* has become " adapted " to a special organism, can of course be administered in disease and D'HERELLE claims splendid results in dysentery, cholera and plague. As, however, different phages may be more or less specific, more or less polyvalent, strong or weak, it is very essential that a careful selection of them should be made for use and especially that they should be of maximal virulence.

The subject of adaptation of the bacteriophage to a bacterium is one of the greatest interest in bacteriophagy. It may, as has been said, be adapted in nature to more than one species, but the acquirement of activity towards one given species is probably the most important characteristic of the phage from the point of view of infective disease.

The course of cholera is, according to the theory propounded, dependent on how quickly the *common* intestinal phage becomes *adapted* to the cholera vibrio in the sense of becoming potent to destroy it. Therapeutic phage must be highly active towards the specific organism. This form of adaptation is brought about by growing the phage, or bringing the appropriate stool filtrate, in contact with young growing organisms of the requisite species. The filtered liquid of these cultures is passed in succession to fresh cultures until the habit of solution or the lytic adaptation is manifest and maximum. It may be well to give D'HERELLE's definition of maximum virulence here, as that exhibited " when a single corpuscle added to a broth tube containing 250 million organisms per c.c. gives complete and permanent dissolution when held at 32°C. Practically speaking this degree of virulence can only be obtained with some Shiga and staphylococcal phages " (BURNET 1930, p. 474). It may be accelerated by using a mixture of the organism for which the phage is originally active with what is called, on analogy with fermentation, the substrate organism. If the phage is originally weakly active to the substrate organism, that activity will be greatly enhanced by passage with that organism alone. Such subpassage of the phage does not necessarily mean loss of other activity. COUVY (1932), however, seems to indicate that lytic power

may at least become restricted as regards range of action on different strains of the same plague bacillus by adaptation. The possible range of action of the phage towards various bacteria, although theoretically indefinite, is actually limited and may even be limited in the case of strictly intestinal bacteria. D'HERELLE with picturesque phrase emphasizes the importance of adaptation as a factor in the struggle for existence of the human being when he says : " Undergo adaptation or die, such is the dilemma confronting all human beings "—and presumably also all bacteria and all bacteriophages. The classification or " typing " of phages as regards range of action of the phage towards groups of individuals *within the species* is especially important in the case of cholera and receives its proper consideration under the head of phage specificity. The question of specific adaptation is complicated by the existence of latency of the lysogenic character in the test organism, by what is regarded as symbiosis and by the occurrence of contamination.

Bacteriophagy and Mutation of Bacteria.

Much might be said on the subject of mutation and the significance of that conception for bacteria. What, however, is evident as regards the relationship of the bacteriophage to this bacterial phenomenon is that the phage is one of the most powerful agents in bringing about the change. Some of the changes brought about are set out by D'HERELLE as :—motility, morphology, capsule formation, mucoid secretion, chromogenesis, proteolytic power, fermentative power, agglutinability, virulence and the formation of filter-passing forms. Almost all of these are exemplified in the case of the cholera vibrio. Dissociation is another term which has to be considered in this connexion, as should also the characters of " roughness " and " smoothness," applied to the colonies resulting from dissociation. The main characters of the rough (R) colony, in contrast to the smooth (S) type, as given by HADLEY (1927), are resistance to bacteriophage lysis, greater viability, increased susceptibility to phagocytosis, sedimentary form of growth in broth, modified antigenic and serological qualities and diminished virulence. Now these are frequently the characters possessed by resistant secondary cultures, which develop in the course of the phenomenon of bacteriophagy. The modifications of character induced by microbic dissociation are, in D'HERELLE's opinion at least, simply induced by the bacteriophage, are proportionate to the resistance of the bacterium, may be reversible and are the visible evidence of a reaction on the part of the bacterium to a pathogenic agent. Mutating or dissociating strains of organisms are not regarded by D'HERELLE as normal strains. They are strains affected by a chronic disease due to the presence of a foreign parasite, in this case the phage. One cannot, however, regard roughness as synonymous with resistance to phage, as is brought out by MORISON (1932 a), who states that Type A phage " seems to be a factor in producing rough, and B & C factors in producing smooth strains." Again he says (1932 b) :—" Vibrios isolated from cases of cholera are usually smooth," but batches were found towards the end of a Calcutta epidemic which were mostly rough and resistant to type A phage. " Such a rough ' A ' resistant vibrio if made resistant to ' B ' or ' C ' types of phage was apparently changed to a smooth strain." So strange is the modification sometimes in the case of the *V. cholerae*, that the appearance of a secondary culture might make one hesitate to identify it on morphological grounds (NOBECHI 1926 b). This is evident also from the statement of D'HERELLE who describes

the extreme resistant stable coccus form obtained by repeated transfers of young secondary cultures of dysentery, typhoid, paratyphoid, coli and cholera organisms as " an organism whose cultural and morphological characteristics are identical with those of the enterococcus." The importance of this theme of dissociation of bacteria is at once appreciable when we point out that the *Vibrio El Tor* has been claimed to be a true cholera vibrio " contaminated " with phage (DOORENBOS, 1932), that is to say symbiotic with and therefore resistant to cholera bacteriophage. Again the *Pasteurella pseudotuberculosis rodentium* is regarded by ZLATOGOROFF and MOGHILEVSKAIA (1928) as a rough (R) form of *Past. pestis*. Thus it may be said that the phenomena of " dissociation " and " bacteriophagy " raise the question of how far cholera-like organisms and plague-like organisms are mutants, or probably better variants, of the organisms which we know as the cholera vibrio and the plague bacillus. Very interesting information on the antigenic structure of *Past. pestis* and *Past. pseudotuberculosis rodentium* is given by SCHÜTZE (1932). HODER (1925) speaks of the definite possibility of transition of *Bact. coli* to paratyphoid-like forms in nature. D'HERELLE affirms that a bacterial strain which is contaminated by phage is recognizable just because it gives, on plating out, mutant colonies. Colonies of an ultra-pure strain are all identical (D'HERELLE, 1926). This statement is denied altogether by HADLEY (1927) as quite insufficient to explain dissociation. The subject of transformation of non-haemolytic to haemolytic organisms, of agglutinating to non-agglutinating, of weak indol producing to strong indol producing is one of great importance in the case of the cholera vibrio. Such transformations are described by SONNENSCHEIN (1930), by BIANCHI and GALLERIO (1931) and by DOORENBOS (1932). The conversion of a non-haemolytic typhoid bacillus to a haemolytic by phage action is regarded by BIANCHI and GALLERIO as being only the intensification of a property which primarily belongs to that organism, " even if it be only in quite a small degree." The application of this doctrine to the cholera vibrio is obvious. PASRICHA, DE MONTE and GUPTA (1931) conclude, for quite a number of characters, that there is some bacteriophage and serological relationship between the true cholera vibrio and the cholera-like forms. Many of these latter they think are mutation forms of the true cholera vibrio and play a great part in the etiology of the disease. D'HERELLE also upholds the doctrine that non-agglutinable, so-called pseudocholera vibrios are altered cholera vibrios which have lost their agglutinating and pathogenic properties under the influence of the phage (1928). But it would be a mistake to imagine that all are in agreement on this subject of transformation of species or mutation. Quite recently MORISON (1931) has especially dealt with the repetition of experiments on change over of " true cholera " agglutinating vibrios to non-agglutinating. His conclusion in this case was that the alteration obtained was probably due to the occurrence of bacterial contaminations.

Specificity and Types of the Bacteriophage.

It may be asserted firstly that the bacteriophage does not appear to have the specificity of the pathogenic bacteria. Whether bacterial species themselves are really good species, however, in the zoological or botanical sense might be argued further. Each phage according to SEIFFERT (1925) has its own circle of action. There is no specific typhoid or dysentery phage. One and the same phage can dissolve typhoid, coli, proteus, etc. BURNET (1933) concludes, from all the

evidence at present available, " that bacteriophages (1) are independent micro-organisms, viruses which are obligate parasites or symbionts of bacteria, and (2) that there are many different types of bacteriophage, which may differ widely in particle size as well as in almost every activity by which a phage can be characterized." With regard to the bacteriophage as an organism, D'HERELLE has definitely pronounced that there is but one species of phage. Under normal conditions it is a parasite of the intestinal bacteria but is capable of a high degree of adaptation to pathogenic organisms. He speaks, however, of " races " of phage, some with " a specificity so strict that they attack but a single strain even to the exclusion of all other strains of the same species. Other bacteriophage races attack all strains of a single species, and, finally, still others attack all strains of several species, sometimes the strains being but very remotely related." A high degree of species specificity was found by SUGINO (1932) in a plague bacteriophage obtained from three laboratory strains of the bacillus, which was inactive even to allied organisms of the pasteurella group. There are fewer characters for bacteriophages than for bacteria by which species can be differentiated, if such species really exist. Morphological differences are obviously excluded in the case of a wholly ultramicroscopic object. The characters which are available for the separation of phages are size, the resistance of bacterial strains to their action and the specificity of the antisera developed towards phage antigen. It is also definitely stated (WOLLMAN 1927) that antibacterial sera have no effect whatever on phage. The two characters, bacterial resistance and phage antigenic specificity, seem to be at all events highly singular and therefore in one sense of the term specific. Absorption tests appear to be of value in separating phages or in differentiating them. Resistant strains of cholera vibrio do not absorb phage, while susceptible strains do (NOBECHI 1926a). These tests, if they have not yet served for the creation of species, have at least been the means of subdividing phages into " races " or " types."

D'HERELLE regards the bacteriophage as possessed of a " mosaic " of virulences, by which is meant a congeries of more or less highly developed lytic potencies towards different bacterial species. Each of these may be enhanced or may be developed by adaptation of the phage towards a specific bacterium. This phenomenon of adaptation is very important and is usually to be observed by growing phages under suitable conditions in a succession of cultures with the organism for which they may have been originally inactive or only weakly active. Theoretically at least it is to be presumed that the bacteriophage could be made lytic by adaptation under suitable conditions to any bacterium.

We may here consider the subject of typing of cholera bacteriophage. The method was introduced by ASHESHOV (1930) and is dependent essentially on the development of resistance in series and the discovery of new bacteriophages for each successively established resistant strain of bacterium. The number of such types would appear to depend largely on the time available to and the industry of observers, always remembering that with each successive addition of a new type or strain further additions become more and more difficult to obtain. The cholera phage types, which have been given letters of the alphabet to distinguish them, have now reached the letter J in the hands of MORISON and his co-workers (1932 a). At the same time, as BURNET (1930) points out, while characteristic differences between phages lysing one organism can often be detected immediately from the

appearance of the isolated plaques, these "remain very constant to type in successive 'generations' of the same phage, but often differ greatly for phages of different origins." The points in which plaques differ are, size, nature of edge, halo and degree of secondary growth. In very brief description the method of phage typing, taken largely from ASHESHOV's and MORISON's descriptions, may be given as :—A number of cholera bacteriophages are, say, isolated in pure line cultures. These are obtained by eliminating other types by a process of dilution from cholera cases on their way to recovery. With one of these a young growing culture of cholera vibrios is inoculated and, after lysis has taken place, a secondary growth of resistant cholera vibrios is obtained. By testing this resistant growth with the other cholera phages some one or more of the latter will be found to lyse this resistant strain and so we get a second type of cholera phage. In the same way a third phage may be obtained and so on. ASHESHOV called his types A, B and C and these seem to be the main types, so far as Indian distribution is concerned. It is contended by ASHESHOV that any bacteriophage which is to be used prophylactically or therapeutically in cholera should contain all three types. "An emulsion of vibrios if acted upon by all the three types of bacteriophage combined is usually destroyed completely unless the bacteriophages are of low virulence." The *caveat* here inscribed with regard to the possibility of low virulence is of great importance therapeutically, for through it we are introduced to the possibility of an administration of phage actually doing harm by insufficient action and to the occurrence of unexpected events in the epidemiology of cholera. PASRICHA, DE MONTE and GUPTA (1932) and MORISON (1932 a) have added to these types.

More than one method may be adopted for the isolation of types and identification of mixtures of phage. In general terms the most certain is that which sets out ribbon cultures, in parallel on agar, of a succession of vibrio strains, each of which has been made resistant to all but one of the standard types of phage available, together with one strain resistant to all the phages. On each of these bands of growth the test and standard phage filtrates are set out, one horizontal row of drops for each of the phages, A, B, C, . . The plates are incubated overnight and then examined. Plaques will be found so distributed as to enable one to judge which bacteriophage is identical with which and whether the test phage is a new one or one already isolated. Very good plates in illustration of this method of testing for types of phage are given by MORISON (1932 a). By this method it is possible to pick out bacteriophages belonging to one of the already isolated types, to diagnose a mixture of types, or to discover a new type. As expressed by MORISON (1932 a) it is the method of using single strains of cholera vibrio made resistant to n types of bacteriophage taken (n-1) at a time with the addition of one strain made resistant to all of the n types in order to detect the appearance of an entirely new type. A new method of determining the type of a phage or of isolating it in pure condition has been devised by ASHESHOV (1933), which is dependent on the high specificity exhibited by antiphage sera. The sera used are called "Minus one Type" sera and each inhibits the development of all the "laboratory types of phage against a bacterium except one which is called the missing type." The technique, for the three phage types A, B, and C, is given by ASHESHOV as :—Mix in each of three small tubes one drop of phage suspension and one drop of the three sera. Incubate overnight. Next day spread a normal culture of cholera vibrio in

a column on agar. When dry, put one droplet from each tube on the spread culture. The result can be read in 8–10 hours. The method of classification of cholera types above described is that of ASHESHOV. BAIL (1923) first used the size of the plaques formed—large, medium, small—provided they show constancy of appearance as one of the differential characters of phages. The plaques characteristic of cholera phage types have other distinctive characters than size to distinguish them. "The plaques of A type have sharply defined margins and inside the plaques there are frequently small bacterial colonies. Those of B type have margins less sharply defined and secondary colonies of the vibrio are not so frequent. Those of C type are frequently surrounded by a halo similar to the halo which SERTIC (1929 a) has shown is due to a lysin, which diffuses out into the agar from the area to which the bacteriophage itself is confined" (MORISON, 1932 a). ASHESHOV's division of bacteriophages into groups consisting of the respective types, "means that each member of each group can act upon and destroy the secondary growth of vibrios which has acquired resistance to the action of a bacteriophage belonging to one of the remaining . . . groups."

Differences of action are observable among the different types of phage. Thus type A is quick to act, unstable, delicate in action and restricted in range of action to "smooth" strains of *V. cholerae*. It is probably much more delicate than has hitherto been thought. The more stable races of this type are not very polyvalent inasmuch as they, at most, attack only about 30 per cent. of freshly isolated cholera vibrio strains (ASHESHOV, ASHESHOV, KHAN and LAHIRI, 1930). "Types B and C are almost omnivirulent. . . . They act even on some non-agglutinable vibrios—a fact deserving great attention" (ASHESHOV, 1931). In the case of plague, COUVY (1932) concludes that the specific character of a bacteriophage has no relation to smoothness or roughness of colonies nor to S and R characters of the organism. In this whole connexion one may refer to the important view of SERTIC (1929 b). According to him bacteriophage suspensions, as isolated, consist of individual phages with different characters; these are variants, which are present in different degrees of numerical proportion: these may be isolated as individuals, that is to say, in the present connexion, types, by plating out the phage suspension upon bacteria partially immunized, thus rendering the plaques of the minority variant visible. In this way there may then be obtained a series of variants which act on resistant secondary cultures of the corresponding bacterial species. The contention again of RAO (1932) is that there can be an infinite number of grades of cholera vibrio with characters ranging continuously from the extreme "smooth" to the extreme "rough." In that case the types of phage which have been isolated and continue to be isolated might conceivably be related to individuals possessing an antigenic constitution describable as a greater or less degree of smoothness or roughness. A discussion of the relation of antigenic structure of organisms and phage action will be found in publications by BURNET (1927, 1930 a and b and 1932). The existence of a number of types of cholera bacteriophage is of the highest importance in connexion with treatment. Mention has been made in this connexion of the specificity of antiphage sera. This is of high degree and extends even to phage types, a proof, according to ASHESHOV (1932) that these types are antigenically differentiated from one another.

[*To be concluded.*]

TYPHUS AND TYPHUS-LIKE DISEASES.

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Introductory.

It seems but a few years since we were accustomed to look upon typhus fever as a definite single entity. This disease had emerged from the welter of jail and famine fevers and the pestilences of armies where previously it had been confused with relapsing fever, typhoid, dysentery and other filth diseases. Typhus fever was regarded as an epidemic contagious disease which spread like wildfire through a country, a city, an army or an institution and destroyed from 30 to 60 per cent. of the people attacked, sometimes even a higher proportion; such epidemics occurred as a rule in the winter among people huddled together for warmth without means of cleanliness or change of clothing either day or night, and people who were suffering from privations and often actual starvation; not only was there an exaltation of the pathogenicity of the virus but also lack of resistance in the attacked. Of later years such devastating epidemics of typhus have but rarely been reported, although the huge epidemics in Serbia and Galicia during the War occur to mind, and since then the disease has continued to smoulder on in Galicia and in Russia and North Africa. On the other hand mild forms of a typhus-like disease have been reported from many countries all over the world.

Nicolle and other investigators demonstrated that typhus fever is conveyed from man to man by the body louse and that in the absence of lice a case of typhus is not of danger to other patients in the same room or ward. This discovery was followed by the discovery of Rickettsia bodies in the vectors.

Definition of Rickettsia. Topley and Wilson (After Cowdry, 1926).—"Gram-negative, bacterium-like objects of small size, usually less than half a micron in diameter, which are found often intracellularly, in arthropods, which may be more or less pleomorphic, which stain rather lightly with aniline dyes but well with Giemsa, and which resemble in most of their properties the type-species *R. prowazeki*."

Brill's disease or Endemic typhus.

In New York in 1898 Brill had first described a mild typhus fever, sporadic in nature and definitely not carried by lice nor spreading in the manner in which lice-borne typhus spreads. This disease was so similar in its clinical manifestations to true typhus, apart from the mortality rate, that when it was shown in 1912 that a guineapig which had reacted with fever to the true typhus virus did not react when subsequently inoculated with the virus of Brill's disease, also that a guineapig which had reacted to the virus of Brill's disease was immune to the virus of the true typhus, *i.e.*, a positive crossed immunity test, it was generally accepted that Brill's disease was merely a mild form of typhus and that the viruses of the two diseases were identical although the vectors might not be the same. Brill's disease was regarded as the inter-epidemic form of typhus. More recently it has been shown that

lice can also be infected by anal injection with the virus of Brill's disease and that Rickettsiae appear in the cells lining the mid-gut of these insects exactly as occurs in true typhus.

Again, the Weil-Felix reaction (agglutination by serum of typhus patients of certain strains (X2, X19) of Proteus originally isolated from cases of typhus) is positive both in Brill's disease and in true typhus.

Endemic typhus and Rodents : Epidemiology.

On epidemiological grounds the association of endemic typhus with rats and grain stores was suggested by HONE (1922) in Australia, and by MAXCY (1926) in America, but the actual experimental proof was not forthcoming until 1931 in America where MOOSER, DYER and co-workers fully and conclusively proved the role of the rat and the rat flea as carriers of the virus. DYER and his co-workers (1931, 1932) collected rats from areas (Baltimore and Savannah) where numerous cases of endemic typhus had occurred. The rats were chloroformed and fleas collected from them. These fleas were identified as *Xenopsylla cheopis* and *Ceratophyllus fasciatus*, the former in the majority. An emulsion was made of these fleas and was injected intraperitoneally into guineapigs ; these animals reacted after an incubation period of four days and developed fever with swelling of the testicles, exactly the same reaction as follows injection of the virus of endemic typhus. About the same time in 1931 MOOSER, RUIZ CASTAÑEDA and ZINSSER in Mexico were able to demonstrate the presence of the endemic typhus virus by means of injection into guineapigs of the brain of wild rats caught in endemic areas. DYER and his co-workers have gone further and have been able to show that *X. cheopis* fleas become infected when fed on infected white rats and can convey the infection to other white rats in separate cages. It has also been shown by the same workers that the virus multiplies in the flea and that the faeces of the fleas are infective. Rickettsia bodies can be demonstrated in the infected fleas. DYER sums up as follows. " The rat flea *Xenopsylla cheopis* as a vector of endemic typhus meets the requirement of the epidemiological evidence."

BRUMPT and other workers in Europe have confirmed DYER'S results but BRUMPT (1932) working in Paris, where endemic typhus has not been recorded for many years, found a higher percentage of rats infected with the virus of endemic typhus than did MOOSER and other American workers in endemic areas. BRUMPT sounds a note of caution and asks, is this virus that we can isolate so readily from wild rats by inoculation into guineapigs a true typhus virus, or is it merely a virus of rats not communicable to man ?

That Brill's disease, endemic typhus, does not spread as does plague is due to the fact that the virus does not remain in the rat for many days and that the rat does not die of the disease, hence the flea populations have not the necessity to seek an alternative host but remain on the rats or in the rats' nests throughout their lives ; in plague the infected rats die and the fleas pass on to other rats which in their turn die and finally fleas are driven to overflow on to man ; some of these fleas are heavily infected with plague bacilli (blocked fleas) ; such a condition of mass infection with Rickettsia does not arise in the flea in endemic typhus.

Relation of endemic to epidemic typhus.

The epidemic spread of louse-borne typhus is due to the fact that no animal host is necessary, the infected lice passing directly from man to

man either on the death of the infected person or driven to transfer from one man to another by reason of the high temperature of the infected person. The lice in epidemic typhus can be shown to be heavily infected with Rickettsia, not so the *Cheopis* flea in endemic typhus.*

This difference in the vector of the two diseases also accounts for the fact that true typhus is a disease of the winter and of crowded insanitary places, whereas Brill's disease occurs in the warm weather and is not necessarily associated with insanitary or crowded humanity except in so far that there is generally a close association with rats and their breeding places. An instance of this is the occurrence of Brill's disease on board the French cruisers in Toulon Harbour; the men sleeping in the tween decks were found to be infected with endemic typhus and rats were discovered to be breeding between the steam pipes which led along these decks, the rats running over the sleeping men in their hammocks at night, the necessary temperature for the multiplication of the fleas and the virus being thus artificially maintained by the steam pipes both in summer and winter.

Other forms of typhus.

In 1910 a mild form of typhus fever similar to Brill's disease was described as occurring in Australia, in North Africa and also in South Africa, and during the War (1916–17) very numerous cases of trench fever, a mild but prolonged fever with rash, were noted and it was demonstrated that this disease was carried by lice and that Rickettsia appeared in infected lice; curiously enough these bodies were found free in the lumen of the alimentary canal and not enclosed in the epithelial cells lining the midgut as are the Rickettsiae in true typhus in the louse.

Little more was heard of these typhus-like diseases for some few years until in 1916 MEGAW described a typhus-like fever in the Kumaon hills in India; he himself suffered from this disease and was of opinion that the disease was carried by a tick (tick typhus). Up to the present (1932) transmission by the tick has not been definitely proved by experiment in India, but PIJPER and DAU in South Africa (1931) fed the larvae of ticks (*Amblyomma hebraeum* and *R. sanguineus*) on a volunteer; ten days later fever developed with intense headache and papular rash (tick typhus, tick-bite fever). The Weil-Felix reaction in this case was carefully tested throughout the fever and during convalescence; twenty-one samples of blood in all were taken and three strains of Proteus, X19, X2 and XK, were used. The titre for all three commenced to rise during the incubation period and reached 1/100 at the beginning of the fever; the peak of the curve was reached on the 22nd day although the fever ceased on the 19th day, reckoned from the date of the bite. The titre for the XK strain was much higher, 1/400, than that for X19 or X2.

Following on MEGAW's suggestion similar diseases were described in Australia by HONE (1922), in the United States by MAXCY and in Malaya by FLETCHER (1925).

Tropical typhus.

Six cases of typhus-like fever occurred in a military camp near Kuala Lumpur, F.M.S., and the officer in medical charge, who recognized

* Rickettsiae are not found in the lumen of the gut in *X. cheopis* owing to the presence of a peritrophic membrane, but they may be numerous in the epithelial cells of the stomach (MOOSER and CASTANEDA, *Bull. of Hyg.*, Vol. 7, p. 354).

these cases as out of the common, called in the aid of the Institute for Medical Research; the cases were thoroughly investigated by the then Director, Dr. W. FLETCHER (1925); other similar cases came to light and FLETCHER was able to show that there were in the Federated Malay States two forms of mild typhus, one occurring in the towns and spreading among people dealing with grain, the other occurring in the country, especially on the plantations, and having a close association with the clearing and pruning of the palm trees.

FLETCHER was also able to separate these two forms of the disease serologically; in the urban disease (Brill's disease, endemic typhus—rat flea) the serum of patients was found to agglutinate the ordinary strains of Proteus, X19 and X2, whereas the serum of the scrub or rural typhus patients did not agglutinate these strains but did agglutinate a variant of X19, the so-called Kingsbury strain XK. The actual vector of scrub typhus has not yet been definitely incriminated but on epidemiological grounds it is probably a mite or a tick.

Japanese River fever can hardly be called a *mild* form of typhus, although clinically it is a typhus-like disease and is known to be carried by a mite; in this disease the serum of the patient agglutinates XK and not X19. In Rocky Mountain fever, a typhus-like disease of high mortality definitely proved to be carried by a tick, in which animal Rickettsiae can be readily demonstrated, the Weil-Felix reaction is positive both with X19 and XK (FELIX). In neither of these diseases is reaction well marked, *i.e.*, a positive reaction is obtained only in low dilutions and it would appear that the reaction is rather of the nature of a group reaction, and until homologous proteus strains are isolated from cases of the two diseases the reaction will continue to be indefinite.

Fièvre boutonneuse: its relation with the typhus group of fevers.

Since 1910 a typhus-like disease has been known to occur on the Mediterranean Littoral, first described by CONOR and BRUCH (1910) in Tunis as "fièvre boutonneuse." It has later been shown to occur also in Marseilles and in many other districts in Southern France; also in Italy, Portugal, Spain, Greece and Rumania where it has been known as "eruptive fever," fièvre exanthématique. This disease has now quite definitely been shown by DURAND and CONSEIL (1930) and BRUMPT (1930) to be carried by the common dog tick *Rhipicephalus sanguineus*, and although it has not yet definitely been decided that the dog is the reservoir of the virus, these animals have been shown to be susceptible and their blood infective for man and monkeys.

In this disease, at the site of the tick bite, there is a primary sore or ulcer, "tache noire," with lymphangitis, just as occurs in tick-bite fever in South Africa (TROUP & PIJPER, 1931) and in Japanese River fever.

French observers are loth to admit that exanthematous fever (eruptive) belongs to the typhus group, and the points of difference stressed by them were that the Weil-Felix reaction was negative and that guineapigs are not susceptible to infection, also crossed immunity experiments with typhus virus were negative.

Male guineapigs infected with the virus of endemic typhus, whether from man, the rat or the flea, react in a typical manner; after an incubation of four or five days fever occurs and later a marked oedema, redness and swelling of the scrotum appears. "The Neill-Mooser reaction," a similar reaction, occurs in guineapigs infected with Mexican typhus virus, but the virus of true typhus (epidemic or Old World

typhus) produces only fever in the guineapig usually without scrotal reaction; so far this reaction had not been obtained with the virus of eruptive fever, but quite recently it has been shown by CAMINOPETROS (1932) in Greece that if an emulsion of infected dog ticks is injected into guineapigs these animals react exactly in the same manner as they do when an emulsion of infected *Cheopis* fleas is injected, *i.e.*, with fever and scrotal reaction; also it has now been shown that the Weil-Felix reaction (X19) is positive in Marseilles fever. These points of difference having been met, this disease can therefore also be associated with the mild typhus-like disease, although it has been shown that the virus of Brill's disease does not protect a monkey from the virus of Marseilles fever or *vice versa*.

According to FELIX (1930) failure to obtain cross immunity between typhus and typhus-like diseases might be due to unequal content of two antigens or to differences in antigen such as occur in serological types of bacteria.

Endemic typhus: *Relation to the vector.*

It is possible that such differences as do exist between these various forms of typhus are due to the differences in vector. For example the virus of Japanese River fever in Japan produces but a mild reaction in guineapigs but the virus of the same disease in Cochin China produces a severe and frequently fatal disease in these experimental animals; if such differences in virulence and behaviour of the virus occur when it is merely a case of a change from one species of mite to another what changes might we not expect when in the one instance the vector is a louse and in the other a flea or, again, a tick. Another instance of the change in the pathogenicity of virus is that of Rocky Mountain or spotted fever; this disease has now been shown to occur in the Eastern States of America as well as in the West; previously in the East the disease had been confused with Brill's disease. Now in the Western type (Rocky Mountain fever) the fatality is high (30 to 50 per cent.), whereas the Eastern type is a mild form of the disease, rarely if ever, fatal, and in this resembling endemic typhus. This change in virulence is possibly due to the fact that a different species of tick is responsible for the conveyance of the disease in the Eastern States.

Rickettsia.

As has already been mentioned, Rickettsia bodies have been demonstrated in the vectors, where known, of these diseases: in the louse, in the tick, in the flea, and in the mite; WEIGL, who utilized a special injection method for infecting lice, employed a very heavily infected fluid from these animals as a Rickettsia vaccine (Weigl) vaccine. He and other workers have shown that if this fluid, rich in Rickettsia, is utilized as an antigen for agglutination tests these small bodies are agglutinated by the serum of convalescents from typhus and not by the serum of normal people. ZINSSER has repeated this work and has found that the peritoneal fluid of irradiated infected rats contains very numerous Rickettsia bodies and that this fluid can also be used as antigen for agglutination tests. ZINSSER employed two viruses, one, that of European typhus, and the other that of Mexican typhus, and he was able to show that the sera of persons recovered from the New World typhus fever agglutinated the Rickettsia derived from the Old World type and *vice versa*, and that the serum of rabbits inoculated with these

two viruses contained agglutinins both for the homologous and heterologous strains of virus. Incidentally the sera of these rabbits inoculated with Rickettsia gave a positive Weil-Felix reaction with strains of Proteus. Rickettsia are difficult to demonstrate in the tissues or fluids of typhus patients but can be readily demonstrated in experimental animals, especially so in the fluid of the infected testicle in guineapigs (endemic typhus), or in Descemet's membrane in the eyeball of infected rabbits (tsutsugamushi disease). It might be mentioned, however, that NICOLLE has shown that when the normal tissue of a guineapig (brain or testicle) is injected into another guineapig Rickettsia-like bodies appear in the tissue fluids of the inoculated animal; this author suggests that Rickettsia-like bodies are normally present in the guineapig and multiply in response to various stimuli.

Factors linking the typhus-like diseases.

It would appear that these different forms of typhus-like diseases are very closely linked together by the following factors.

(1) The clinical picture, fever, rash and nervous symptoms; mild cases of Japanese River fever cannot, on clinical grounds, be differentiated from exanthematous (eruptive) fever, nor can the Eastern states type of spotted fever be distinguished from endemic typhus on the clinical picture alone.

(2) During the course of these fevers or in convalescence a positive Weil-Felix reaction can be demonstrated with one or other of the known strains of Proteus.

(3) Rickettsia bodies have been demonstrated in experimental animals which have been inoculated with the viruses of these diseases and/or in the insect vectors.

(4) In the diseases of the group in which careful investigation has been made a common histo-pathology has been disclosed.

Endothelial proliferation in and "typhus nodules" around the smaller capillaries of the skin, the brain or other organs have been demonstrated. It is true that in guineapigs inoculated with the virus of epidemic typhus the lesions in the brain substance, "cell glioses," are much more numerous than in the brain of an animal inoculated with the virus of the endemic disease, yet here also typical lesions can be discovered if carefully looked for. For these reasons and especially on account of the positive agglutination tests with Proteus and Rickettsia it seems but right that these types of endemic typhus should be included in one group. There is evidence to suggest that such differences as do exist between the different types are due to differences in the vector rather than in the virus.

From the public health point of view it is essential, however, that a sharp differentiation should be drawn between such endemic diseases and epidemic or true louse-borne typhus fever, The endemic disease is not spread directly from man to man, whereas epidemic typhus is. Endemic typhus is not and need not be notifiable, epidemic typhus should always be so. In the one case we have a disease of domestic animals or of small rodents only occasionally and incidentally conveyed to man, in the other case a disease conveyed directly from man to man by a parasite of man and spread in epidemic fashion. In the one case a series of broken links, in the other a continuous chain.

A table of the differences between the forms of typhus described in this review is reproduced on p. 406 of this number at the end of the "Typhus and Unclassed Fevers" Section.

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YELLOW FEVER.

STEFANOPOULO (G. J.). Sur la détermination des foyers d'endémicité amaril. [**The Identification of Endemic Centres of Yellow Fever.**] —*Bull. Acad. Méd.* 1933. Jan. 3. 97th Year. 3rd Ser. Vol. 109. No. 1. pp. 26–34.

An interesting account of the author's investigations on yellow fever endemicity in the French West African colonies. Collections of sera were made in various localities, the specimens being kept in the ice chest, and brought back to the Pasteur Institute, Paris, where the necessary tests were made.

The serum to be tested was mixed with neurotropic mouse virus and after being in contact for 15 to 20 minutes at room temperature, small quantities of the mixture were inoculated intracerebrally into mice. Examples are given of some of the results obtained by the use of this test. In a dockyard where two cases of yellow fever among Europeans had occurred, the sera of 11 out of 21 natives were positive, including two children of 7 to 12 years old. Various other examples are given of the use of this test for studying the spread of the disease along lines of communication; to decide where epidemics have occurred previously; to determine whether the disease has disappeared from an endemic centre and the efficiency of measures of control; and to decide whether or not cases of the disease are really localized and introduced as, for example, the small epidemic of Grand Bassam.

Finally the sera of 21 Europeans living in regions affected by yellow fever epidemics were examined, with negative results, in marked contrast with the high percentage of positive results obtained with the sera of natives from the same localities. It would seem, therefore, that mild unrecognized cases of the disease are rare in Europeans though common among the natives.

With regard to yellow fever in French West Africa the author recognizes 4 regions: (1) Where the disease has long been absent; these must be protected. (2) Where only isolated cases of the disease have occurred. (3) Regions with frequent epidemics requiring particular attention. (4) Regions which constitute endemic foci.

E. Hindle.

DURIEUX (C.). Enquête sur la fièvre jaune dans les colonies du Niger, du Soudan et du Dahomey. [**Yellow Fever Inquiry in the Colonies of Niger, Soudan and Dahomey.**]—*Ann. Inst. Pasteur.* 1932. Dec. Vol. 49. No. 6. pp. 736–742. With 4 figs. on 2 plates & 1 map.

A general account of a tour of these three West African Colonies by members of the West African Rockefeller Commission under Dr. MAHAFFY, accompanied by the author. Collections of serum and mosquitoes were made at various places, and the results confirm the view that yellow fever occurs in the native population. *E. H.*

BEEUWKES (Henry), KERR (J. A.), WEATHERSBEE (A. A.) & TAYLOR (A. W.). **Observations on the Bionomics and Comparative Prevalence of the Vectors of Yellow Fever and Other Domestic Mosquitoes of West Africa, and the Epidemiological Significance of Seasonal Variations.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1933. Mar. 23. Vol. 26. No. 5. pp. 425–447. With 5 figs.

In connexion with numerous epidemiological and entomological studies on yellow fever in West Africa, the authors undertook in 1930

an intensive survey of four large towns, Lagos and Ibadan in Southern Nigeria, and Kano and Zaria, in Northern Nigeria, and in addition a small village of 50 houses, Wallidazene, 110 miles east of Kano. Particulars are given of conditions in these localities that may be of interest in connexion with the epidemiology of yellow fever, followed by a section devoted to the index of breeding and mosquito population.

The index of breeding was found to be much lower in Lagos than in any of the other towns studied whilst Ibadan had the highest index. The differences between Ibadan and Lagos can be attributed directly to the piped water supply and efficient sanitary service in the latter. The lower indices of Kano and Zaria, as compared with Ibadan are probably due to the different meteorological conditions, since there is no sanitation in these towns which would effectively control the carriers of yellow fever. On the other hand the mosquito population of the northern towns as compared with house and container indices was very low, indicating that in the north the length of life of Aëdes is relatively short. It is shown that there is a high mosquito population in the north, and during the rainy season conditions favour the longevity of the insects and epidemics of yellow fever may occur, but it is doubtful whether the infection can persist through the usual harmattan season and the extensive epidemics of 1931 were only made possible by the failure of the harmattan in the early part of the year. In the north large numbers of *Mansonia africana* were captured in the houses and in Kano actually outnumbered *Aëdes aegypti* ; consequently that species must be regarded as possibly of some epidemiological significance as a carrier. With the exception of these and 5 *Culex thalassius*, taken in Lagos, none of the species proved experimentally to be possible carriers, were found in any of the houses.

Longevity experiments with *Aëdes aegypti* were carried out at Yaba in the south, and Gadau in the north. The results show that the length of life does not vary to any great degree in the uniform climate of Southern Nigeria, but in the north it is only during the rainy months of June to September that the length of life approximates to that in the south. During the cold harmattan season when relative humidity was about 30 per cent. in the laboratory, insects kept in a moist chamber at 60 per cent. humidity die as quickly as those in the laboratory. At Gadau, in five experiments, under ordinary room conditions, males lived for maximum periods of 26 to 75 days with means of 10 to 43 days ; the females for maxima of 45 to 109 days and means of 22 to 65 days. When kept in a moist chamber the males lived 61 to 91 days with mean lengths of 29 to 46 days ; and the females 116 to 169 days, with means of 49 to 86 days. *E. H.*

Mazza (Salvador). Comprobacion de focos de fiebre amarilla en el departamento de Santa Cruz, Republica de Bolivia. [**Foci of Yellow Fever in Santa Cruz Department, Bolivia.**]—Universidad de Buenos Aires Misión de Estudios de Patología Regional Argentina, Jujuy. Publicación No. 9. 28 pp. With 2 maps in text. 1932.

It is shown in this paper that yellow fever was present in Bolivia, not far from the Argentine border, in 1932.

On the night of the 19th April, 1932, the Commandant of the Fifth Division of the Argentine Army received the startling news that 60 per cent. of the troops belonging to a regiment of the Bolivian army stationed in the town of Santa Cruz de la Sierra, the capital of the

Department of Santa Cruz, had been attacked by yellow fever and that 75 of the civil population had fallen victims to this disease. A commission was forthwith appointed to investigate.

The regimental medical officer informed them that 60 per cent. of the soldiers had showed fever with severe jaundice and he diagnosed paratyphoid. The grounds for this are obscure since his description of symptoms was as follows: malaise, severe headache, furred tongue, epigastric pain, frequent vomiting or diarrhoea; then an afebrile period with marked debility, depression and gastric irritability. Some then began to improve, others had repeated haemorrhages, from nose, stomach, intestine, with jaundice and pain over the liver, preceding death and at autopsy the liver showed acute yellow atrophy.

Another local medical man who saw these cases diagnosed yellow fever or Weil's disease. Investigations revealed that 59 soldiers had been attacked and 4 had died, that there had been altogether 92 patients and 8 deaths. A history was given that "at a certain time of the year climatic fever attacked persons who came down from the hills or provincial districts."

Sera of some of those who recovered were sent to the Oswaldo Cruz Institute for the protection test to confirm or disprove yellow fever and sections of the liver from post-mortem cases for the changes associated with yellow fever. *Aëdes aegypti* were found in considerable numbers in and about the houses. Six of the sera were tested for agglutination of *L. icterohaemorrhagiae* with negative results; they, however, gave protection to *M. rhesus* against yellow fever virus and the liver tissues sent showed the characteristic changes. One patient gave strong agglutination of *Bact. typhosum*, another agglutinated *Proteus* X 19 and he gave a history indicative of a previous attack of typhus. A map is reproduced showing the localities where yellow fever had been reported in an outbreak in 1887. Another map of Bolivia in 1925 is so reduced as to be indecipherable; half of it resembles a letter from the War Zone obliterated by the censor. The result of the investigation, however, has been to show that by pathological changes in the liver, by protection tests with the serum of recovered patients and by fixation of complement reactions, absence of *L. icteroides* by direct examination and inoculation experiments, yellow fever is endemic in Santa Cruz de la Sierra. *H. H. S.*

Hoffmann (W. H.). **Epidemic and Endemic Yellow Fever.**—*Jl. Trop. Med. & Hyg.* 1932. Dec. 1. Vol. 35. No. 23. pp. 359–363.

A valuable article on the importance of yellow fever from the point of view of public health.

The author considers that the measures hitherto employed, although effective in epidemics, are not sufficient to control yellow fever in its endemic areas. Moreover in spite of all warnings the situation is more serious to-day than ten years ago, for owing to changes in the political and social order of many parts of the world, there has been a neglect of hygienic measures which might well open the way for a great pandemic. It is essential that there should be international co-operation in a campaign against the disease, and what is especially needed are reliable periodic reports of the current state of endemic and epidemic infection all over the world. Finally every effort should be made to limit the disease to its two endemic foci, making them smaller and smaller, and aiming eventually at their eradication. *E. H.*

STEFANOPOULO (G.) & CALLINICOS (G.). Dengue et fièvre jaune. Le problème du typhus amaril en Méditerranée. [**Dengue and Yellow Fever. The Yellow Fever Problem in the Mediterranean.**] —*Giorn. di Batteriol. e Immunol.* 1932. Dec. Vol. 9. No. 6. pp. 972–977. [11 refs.]

A general summary of possible immunological relationships between these two diseases.

The authors also give particulars of experiments with the neurotropic virus in mice confirming previous observations which indicate that inoculation with dengue virus does not confer immunity against yellow fever, and moreover that the serum of recovered dengue patients has no action on yellow fever virus. It is also noted that one of the authors, in French West Africa, has found that there have been many victims of yellow fever in a country where dengue still exists.

With regard to the Mediterranean, the authors are of the opinion that the persistence of dengue in coastal regions denotes a possible risk of the appearance of yellow fever. *E. H.*

PHILIP (Cornelius B.). **The Experimental Transmission of Yellow Fever by Mosquitoes.**—*Science.* 1930. June 13. Vol. 71. No. 1850. pp. 614–615.

The author refers to unpublished tests with *Aëdes* (*Aedimorphus*) *irritans* and *Aëdes* (*A.*) *nigricephalus*, as well as of *Aëdes* (*Banksinella*) *punctocostalis* and *Culex thalassius*, all of which were found to contain yellow fever virus after the elapse of adequate incubation periods following an infecting meal. Although these insects failed to produce infection by their bites, when ground up in saline and injected into normal monkeys they produced fatal infections. *E. H.*

DAVIS (Nelson C.). **Attempts to transmit Yellow Fever Virus with *Triatoma megista* (Burmeister).**—*Jl. Parasitology.* 1933. Mar. Vol. 19. No. 3. pp. 209–214.

The injection into rhesus monkeys of *Triatoma megista* that had ingested infected blood produced yellow fever when the interval was three to six days; after an interval of seven days fever followed by immunity; after eight and ten days no fever, but immunity; and after fourteen days neither fever nor immunity. It is evident, therefore, that there is a gradual dying out of the virus. Faeces collected at various intervals were non-infective.

In one instance yellow fever was transmitted mechanically by the bites of triatomas after an interrupted blood meal on an infected animal. After longer intervals comparable to the extrinsic incubation period in mosquitoes, the bites failed to infect. *E. H.*

LAIGRET (J.). Sensibilité de certaines souris sauvages au virus de la fièvre jaune. [**The Susceptibility of Some Wild Rodents to Yellow Fever Virus.**]—*C.R. Acad. Sci.* 1933. Feb. 13. Vol. 196. No. 7. pp. 508–510.

Mus musculus musculus, the ordinary grey house mouse, and *Mus musculus gentilis*, an African variety, were found to resemble the white mouse in being susceptible to yellow fever virus if inoculated intracerebrally, but not to intraperitoneal injections. Another African

variety, however, *Mus musculus azoricus*, Schinze, was found to be susceptible to intraperitoneal injections of the neurotropic mouse virus.

Two out of three mice died from the infection after 5 days and the third was killed and used for further inoculations. An emulsion of the abdominal viscera of this animal into white mice produced typical encephalitis when inoculated intracerebrally but was without effect when given intraperitoneally. It is conceivable that this mouse might be infected with yellow fever virus in nature. *E. H.*

Stefanopoulo (G.). Sur le virus amaril d'origine murine inoculé à *Macacus rhesus*. [**The Inoculation of *Macacus rhesus* with Mouse Yellow Fever Virus.**]—*Bull. Soc. Path. Exot.* 1932. Oct. 12. Vol. 25. No. 8. pp. 866–869.

A monkey inoculated intracerebrally with mouse yellow fever virus, after 16 passages in mice, was killed *in extremis* on the seventh day with typical symptoms of ordinary yellow fever. A second monkey inoculated subcutaneously with a liver suspension of the first monkey, died of typical yellow fever on the 12th day. Four monkeys were inoculated with a mouse virus after 21 to 31 passages in mice, whilst another four monkeys with another strain of mouse virus after 145 to 161 passages in mice. The former was found to persist longer and more constantly in the blood of the monkeys than the latter. Mosquitoes fed on a monkey infected with a mouse strain after 21 passages in mice were fed after intervals of 17, 21 and 22 days on two monkeys which both became infected with non-fatal yellow fever. A similar experiment with virus after 147 passages in mice gave negative results.

E. H.

Lloyd (Wray) & Penna (H. A.). **Studies on the Pathogenesis of Neurotropic Yellow Fever Virus in *Macacus rhesus*.**—*Amer. Jl. Trop. Med.* 1933. Jan. Vol. 13. No. 1. pp. 1–45. With 6 figs. [16 refs.]

An interesting study of the pathogeny in monkeys of a neurotropic strain of the virus which has been passaged by intracerebral inoculations in mice for three years with more than 200 passages.

Three monkeys inoculated intracutaneously with a suspension of infected mouse strain showed reactions at the site of inoculation and two of them developed fever. All these animals were subsequently found to be immune. Monkeys inoculated either subcutaneously or intraperitoneally frequently showed fever and were immunized against yellow fever, and often virus could be recovered from the circulation. Attempts were made by such passages in monkeys to re-establish the viscerotropic properties of the virus, but without success.

Two monkeys were inoculated into the sciatic nerve with suspensions of virulent mouse virus. Both of these animals had 5 to 6 days of fever after intervals of 17 and 22 days respectively, and were found to have been immunized. One was tested against the ordinary viscerotropic virus and the other inoculated intracerebrally with neurotropic virus but neither of them showed any reaction.

When normal monkeys were inoculated intracerebrally or intraspinally with the neurotropic virus they developed a characteristic encephalitis with definite pathological lesions, but the animals inoculated intraspinally showed longer incubation periods than those

inoculated into the brain. Monkeys that had recovered or been immunized against yellow fever were unaffected by injections of the neurotropic virus. As in the case of mice, monkeys dying of yellow fever encephalitis showed the presence of virus in the brain, spinal cord and peripheral nerves, also in the retina, salivary glands and adrenals. At death the virus was absent from the blood, spinal fluid, liver, kidney, pancreas and spleen.

The pathological changes in the central nervous system were widespread infiltration of mononuclears and lymphocytes in perivascular concentrations and in diffuse disseminations throughout the central nervous system. As a rule the infiltration was most marked in the regions of the basal ganglia and brain stem. Degenerative changes occur in the neurone cells of the cerebral cortical gyri, brain stem and spinal cord.

The neurotropic strain of virus after passage in the nervous system of monkeys for seven months still retained its characteristic properties and when tested in mice was indistinguishable from the strains that had been maintained exclusively in mice.

Typical yellow fever encephalitis was also produced by the inoculation of the neurotropic virus into other species of animals including the Asiatic monkey *Macacus cynomolgus*, the African *Cercopithecus tantalus*, the South American *Saimiri sciureus* and *Ateles paniscus*, and in certain marmosets, as well as at least two rodents, the guineapig and the agouti.

A Berkefeld N filtrate of the neurotropic virus in normal saline containing 10 per cent. serum was found to be infective to monkeys, and such filtrates were found to retain their properties when dried *in vacuo* in the frozen state. *E. H.*

Roubaud (E.) & Stefanopoulo (G.). Recherches sur la transmission par la voie stégomyienne du virus neurotrope murin de la fièvre jaune. [**Studies on the Mosquito Transmission of Neurotropic Yellow Fever Virus.**]—*Bull. Soc. Path. Exot.* 1933. Feb. 8 & 9. Vol. 26. No. 2. pp. 305–309.

An independent confirmation of the fact that neurotropic yellow fever virus after numerous passages in mice is not easily transmitted by mosquitoes. However, the presence of virus for several days in the circulation of inoculated animals shows that great care is essential in using this virus for the vaccination of human beings. *E. H.*

Davis (Nelson C.), Lloyd (Wray) & Frobisher (Martin), Jr. **The Transmission of Neurotropic Yellow Fever Virus by Stegomyia Mosquitoes.**—*Jl. Experim. Med.* 1932. Dec. 1. Vol. 56. No. 6. pp. 853–865.

Using the French strain of neurotropic virus in mouse passages from the 149th to the 181st, the authors infected both rhesus monkeys and mice in order to determine whether it was possible to transmit the virus through mosquitoes.

The insects were allowed to feed on monkeys 24 to 48 hours after the inoculation and mice after intervals of 2 to 24 hours. Although circulating virus was present in every animal when bitten by the mosquitoes, only rarely did these insects produce infection when subsequently fed on normal monkeys or mice. Mosquitoes that had acquired their infection by feeding on an infected monkey were fed on

6 mice 2 weeks old, and three became ill with encephalitic symptoms and were shown to contain the neurotropic virus. It is evident, however, that this fixed neurotropic strain cannot be maintained in mosquitoes as well as can the viscerotropic strains. Even after passage through mosquitoes there was no evidence of the reversion of the neurotropic virus to the original type and it is evident that the virus has changed fundamentally as a result of its passages in mice. *E. H.*

Mathis (Maurice). Sur le pouvoir infectant des *Macacus rhesus* vaccinés contre la fièvre jaune. [**The Infective Capacity of *Macacus rhesus* Vaccinated against Yellow Fever.**]—*Bull. Soc. Path. Exot.* 1933. Feb. 8 & 9. Vol. 26. No. 2. pp. 310–313.

Monkeys inoculated subcutaneously or intraperitoneally with neurotropic virus, after 140 passages in mice, were found to contain virus in the circulating blood from 19 hours after inoculation up to 12 days. Attempts to infect *Aëdes aegypti* by feeding on these monkeys gave negative results. *E. H.*

Cruz (J. da Costa) & Villela (Gilberto G.). L'alexine et le fibrinogène dans l'intoxication chloroformique et dans la fièvre jaune. [**Complement and Fibrinogen in Chloroform Intoxication and in Yellow Fever.**]—*C. R. Soc. Biol.* 1933. Mar. 10. Vol. 112. No. 9. pp. 915–917.

The authors find that chloroform intoxication differs from yellow fever in its relative effect on the complement and fibrinogen content. In the former a reduction of the complement to a seventh or eighth of its original concentration was accompanied by a reduction of the fibrinogen to about one-tenth. In the case of a monkey infected with yellow fever the complement fell to about one-fifth, and the fibrinogen content only to about half the original concentration. It is concluded that the fall in the amount of complement in cases of yellow fever is not due simply to liver insufficiency, but also to a fixation of the complement *in vivo* by a complex antigen antibody. *E. H.*

Wakeman (A. Maurice) & Morrell (Clare A.). **Chemistry and Metabolism in Experimental Yellow Fever in *Macacus rhesus* Monkeys. VI. The Bromsulphalein Liver Function Test and the Van den Bergh Reaction.**—*Arch. Intern. Med.* 1932. Dec. Vol. 50. No. 6. pp. 876–883. With 2 charts. [10 refs.]

The authors find that the rate of excretion of bromsulphalein dye by the liver is greatly diminished in yellow fever, an abnormal retention of the dye often occurring several days before death. The onset of jaundice is manifested by an increase in the bilirubin content of the blood and increased retention of bile pigment may begin several days before death.

The increasing amounts of bile pigments in the blood and the abnormally slow removal of bromsulphalein dye from the blood are the first indications of the loss of hepatic function in infected monkeys. There is usually an increased clotting time associated with a lowered fibrinogen content of the blood. Acetone is not excreted by monkeys dying of yellow fever, a fact which supports the view that the liver is the chief site of acetone formation.

[No reference is made to KERR's observations on the use of the bromsulphalein test and icterus index in yellow fever (see this *Bulletin*, Vol. 28, p. 722).] *E. H.*

HAAGEN (E.). Weitere Untersuchungen ueber das Verhalten des Gelbfiebervirus in der Gewebekultur. [**Further Studies on the Persistence of Yellow Fever Virus in Tissue Culture.**]—*Zent. f. Bakt.* I. Abt. Orig. 1933. Mar. 31. Vol. 128. No. 1/2. pp. 13–21.

The author has continued to maintain the virus of yellow fever in tissue culture [this *Bulletin*, Vol. 29, p. 577] and gives details of experiments showing that after more than 100 passages there are no appreciable changes in the properties of the virus. In spite of various attempts it was found impossible to grow the virus in the absence of living cells. The virus was found to be rapidly neutralized by the action of immune serum in the presence of living cells, but when the virus had become intracellular, it was able to withstand the action even of concentrated immune serum without being affected. *E. H.*

POSTMUS (S.). De leucocytenformule bij gele koorts. [**The Leucocyte Formula in Yellow Fever.**]—*Nederl. Tijdschr. v. Geneesk.* 1933. Apr. 1. Vol. 77. No. 13. pp. 1391–1396. With 3 figs. English summary.

Rhesus monkeys infected with yellow fever were found to show two types of changes in the leucocyte curve.

(1) In fatal cases, there was an increase in the number of polynuclear neutrophile leucocytes, and a decrease in the number of lymphocytes ; the eosinophiles disappeared after the fourth day of illness and did not reappear.

(2) In cases which recovered the reverse changes took place, the polynuclear leucocytes showing a steady decrease. Other groups of leucocytes showed less distinct variations, but the eosinophiles did not disappear. If human cases show similar changes these results may furnish an explanation of the conflicting reports on the blood changes in yellow fever. *E. H.*

ARAGÃO (Henrique de Beaurepaire). Vaccinações contra a febre amarella. [**Vaccination against Yellow Fever.**]—*Brasil-Medico.* 1933. Feb. 4. Vol. 47. No. 5. pp. 75–80.

A fresh method of vaccination against yellow fever is described.

Before presenting in detail the results of his own experiments in 5 individuals the author refers to the four methods of vaccination hitherto employed : 1. Injection of 2–4 cc. of the serum of man or rhesus immune to yellow fever, followed 24 hours later by 0·1 cc. of virulent blood from an infected rhesus (Aragão). 2. Inoculation of a mixture of immune human or animal serum and yellow fever virus, the blood of an infected rhesus (Aragão, HINDLE and FINDLAY). 3. Injection of human immune serum followed after an interval by a mixture of serum and cerebral virus of the camondongo (Brazilian house-rat), in the proportion of 0·3 cc. serum per kilo. body weight and 0·003 cc. of virus per kilo. (SAWYER, KITCHEN & LLOYD). 4. Injection of cerebral virus of the camondongo, pure without attenuation or previous treatment with

anti-yellow fever serum. Immunization was produced in rabbit, goat, calf and is proceeding in sheep and horse, by injection of increasing amounts of virulent blood.

The author next records in detail five persons, one man and four women, who were treated with camondongo cerebral virus after a test to show that their serum prior to injection possessed no protective property against yellow fever.

The first, a woman of 45 years, received 0·001 gm. of the fresh virus with 4 cc. of the serum of persons who had had yellow fever in 1928 and 1929. Blood taken from her a week later was found infective for camondongos, but after a month was protective for rhesus. The second person, a woman of 20 years, was treated in the same way and she gave the same results except that the systemic reaction to the injection, present in the former was absent. The procedure was slightly modified in the case of the third, a woman of 35 years, with a view to minimizing reaction. She was given 3 cc. of the mixed sera of 4 persons immune to yellow fever, and 6 hours later 2 cc. of the same serum together with 0·001 gm. of virulent camondongo brain. The highest temperature thereafter was 37·4°C. except once on the third day when it reached 38·6° with an attack of vomiting. A month later 2 cc. of her blood protected a rhesus against 0·001 cc. of virulent rhesus blood. The effect of revaccination was observed in this patient by inoculating 0·001 gm. of the camondongo virus two months after the former. There was no reaction produced although the pure virus was inoculated. Patient 4, a woman of 45 years, was inoculated by the same method as the last ; a month afterwards her serum in a dose of 2–4 cc. failed to protect a rhesus, but 6 cc. was effectual, the immunization was less strong. She was then revaccinated in the same way as the primary vaccination of No. 1 and a month later 2 cc. of her serum protected a rhesus against a dose of 0·001 cc. virulent blood. The fifth, a man of 36 years, was treated in the same way as No. 4 and his serum 6 weeks later protected a rhesus when injected in a dose of 2 cc.

To epitomize : The author has recorded a simple but efficacious method of vaccinating prophylactically against yellow fever, without the danger incurred from the use of pure virus and without producing systematic febrile reaction, by injecting intramuscularly into the deltoid 3 cc. of the mixed serum of four persons recovered from the disease and 6 hours later inoculating subcutaneously 2 cc. of the same serum together with 0·001 gm. of the fresh virulent brain of a camondongo. If the larger animals are satisfactorily immunized the use of serum of human recovered cases can be replaced by that of these animals. *H. H. S.*

Scott (R. R.). **The Yellow Fever Problem as it Affects Tanganyika Territory ; together with Notes on Recent Literature on Yellow Fever.** —*East African Med. Jl.* 1933. Jan. Vol. 9. No. 10. pp. 283–293. [17 refs.]

A general account of the subject with special reference to the possibility of yellow fever being introduced into Tanganyika. *E. H.*

Moulinier (M. R.). La fièvre jaune, proche danger. [**The Imminent Danger of Yellow Fever.**]—*Jl. Méd. de Bordeaux.* 1933. Mar. 31. Vol. 110. No. 9. pp. 251–253. With 1 map.

A paper calling attention to the spread of yellow fever in recent times, and the ways in which modern methods of communication favour the spread of the disease. *E. H.*

Sellards (A. W.) & Laigret (J.). Immunisation de l'homme contre la fièvre jaune par l'inoculation du *virus de souris*. [**The Immunization of Man against Yellow Fever by the Inoculation of Mouse Virus.**]—*Arch. Inst. Pasteur de Tunis*. 1932. Dec. Vol. 21. No. 2. pp. 229–238.

A more detailed account of the method of protection against yellow fever previously recommended by the authors [see this *Bulletin*, Vol. 29, p. 572].

E. H.

Bulletin Office International d'Hygiène Publique. 1933. Jan. Vol. 25. No. 1. pp. 46–64. [28 refs.] Connaissances récemment acquises sur la fièvre jaune. (Rapport de la Commission de la Fièvre Jaune de l'Office International d'Hygiène publique, présenté au Comité permanent par le Colonel S. P. James.)

The English version of this paper will be found at pp. 265-277 of No. 5 of this *Bulletin*. *A. G. B.*

Erratum.

No. 1, page 4, Kerr summary. The words " after an extrinsic incubation period of 12 to 18 days " should be deleted.

RELAPSING FEVER AND OTHER SPIROCHAETOSES.

ATKEY (O. P. H.). La fièvre récurrente au Soudan pendant l'année 1931. [**Relapsing Fever in the Sudan during 1931.**]—*Bull. Office Internat. d'Hyg. Publique.* 1932. Nov. Vol. 24. No. 11. pp. 1861–1864.

Epidemics of this disease have continued in the provinces of the Blue Nile and Khartoum, and also there were two small epidemics in Darfur attributed to immigrants from French territory. There was a total of 492 cases with 66 deaths, compared with 386 cases the previous year. The blood of the patients was examined for spirochaetes every other day but only 35 per cent. were positive.

The use of antimony tartrate for treatment has been abandoned, and the author found that the intramuscular injection of 1 cc. grey oil gave slightly better results than the use of novarsenobillon. [See also this *Bulletin*, Vol. 29, p. 805.] *E. Hindle.*

MAURICE (G. K.). **The Entry of Relapsing Fever into the Sudan.**—*Sudan Notes & Records.* 1932. Vol. 15. Pt. 1. pp. 97–118. With 7 figs. on 4 plates.

A general account of the author's personal experiences during the great epidemic of louse-borne relapsing fever in Darfur in 1926. This epidemic killed nearly a quarter of the Fur population of the Sudan, and the economic and political results of the outbreak are described from the point of view of a medical officer who was concerned with the detection of the disease and carried out observations during the subsequent six months. *E. H.*

ROBERTSON (R. Cecil). **Relapsing Fever in Shanghai (First Report).**—*Chinese Med. Jl.* 1932. Sept. Vol. 46. No. 9. pp. 853–885. With 3 charts & 7 figs. on 4 plates. [18 refs.]

A general discussion of relapsing fever in China, with special reference to Shanghai. The number of cases admitted to the Lester Chinese Hospital, Shanghai, during the past four years has been respectively 31, 56, 50 and 234, the latter being the figure for only part of 1932. The majority of the cases occurred in the months April to July.

Interesting particulars are given on the epidemiology of the disease with special reference to predisposing causes, and it is shown that the prevalence of relapsing fever in endemic areas could be readily controlled by the application of existing Public Health knowledge. The clinical symptoms resemble those of the European strain of *S. recurrentis*, and the prognosis is good, except in undernourished patients. Intravenous injections of novarsenobillon in doses of 0·007 gm. per kilo body weight were found to cause disappearance of the spirochaetes and there were no relapses if the drug was given on the third day of fever and before the crisis. If given before the third day or when the temperature was falling relapses often occurred. Stovarsol was also used with success in a few cases.

Careful laboratory investigations of the spirochaete are recorded. The organism was successfully cultivated in various nutrient media, the best results being obtained with human serum containing 0·1 cc. of glucose Ringer's solution to each 1 cc. of serum, covered with a layer of liquid paraffin and the tubes kept at room temperature.

All the patients were infested with lice, and 15 per cent. of these lice were found to contain spirochaetes which reproduced the infection in mice. Various serological and immunological observations are recorded and by the use of the adhesion test it is hoped to be able to differentiate the strains of spirochaetes.

Particulars are given of a seven-day-old child which died with a very heavy infection of relapsing fever. The mother was infected at the time of birth and from the evidence there seems to be little doubt that in this instance the infection occurred *in utero*. *E. H.*

Dunn (Lawrence H.) & Clark (Herbert C.). **Notes on Relapsing Fever in Panama with Special Reference to Animal Hosts.**—*Amer. Jl. Trop. Med.* 1933. Mar. Vol. 13. No. 2. pp. 201–209.

A general account of human relapsing fever in Panama, which has been known to be endemic since 1905, when it was first recorded from this locality.

Since only 117 cases have been diagnosed in the Canal Zone hospitals during the years 1905 to 1930 inclusive, these figures must be only a small fraction of the total number of cases in the country for they represent only Panama Canal employees and their families, or those able to pay for treatment in these hospitals. The disease is known to be endemic in the adjoining country of Colombia and in both countries *Ornithodorus venezuelensis* and *O. talaje* are prevalent and have been shown to be efficient carriers. Both these ticks are commonly collected from rats and other mammals, and in the routine examination of these animals naturally acquired spirochaetal infections have been found which seem to be identical with the human infection. The animals in question are marmoset monkeys (*Leontocebus geoffroyi* Pucheran), opossums (*Didelphis marsupialis etensis* Allen), armadillos (*Dasypus novemcinctus fenestratus* Peters), calves and a horse.

The infection in monkeys has been successfully transmitted to man, white rats, white mice and various species of monkeys [see this *Bulletin*, Vol. 29, p. 208]. Out of 61 opossums many were infested with larvae of *Ornithodorus talaje* and six showed spirochaetes in the blood, which were readily transmissible to marmosets, white rats and white mice. Two out of 31 banded armadillos were naturally infected and two others inoculated with the human strain were readily infected, one of them dying nine days later. Two out of six calves about a month old also showed spirochaetes which were transferred to a marmoset, monkey and white rats. Spirochaetes were also found in the blood of a horse. It would seem, therefore, that the mammals occurring in Panama may serve as a reservoir for the tick borne variety of human relapsing fever. *E. H.*

Porter (Giles S.), Beck (Dorthy) & Stevens (I. M.). **Relapsing Fever in California.**—*Amer. Jl. Public Health.* 1932. Nov. Vol. 22. No. 11. pp. 1136–1140.

A useful summary of the 30 cases of relapsing fever recorded up to date (August, 1932) from the State of California.

Evidence is presented showing that wild rodents may harbour the spirochaetes, for the inoculation of their blood into white mice has resulted in obtaining the infection from nine chipmunks and two

squirrels. Whether the rodents act as a reservoir, or merely become infected from the ectoparasite which also transmits the infection to man, has not yet been determined. *E. H.*

RUSSELL (Helen). **The Pathology of the Spleen in Relapsing Fever.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1932. Nov. 30. Vol. 26. No. 3. pp. 259–265. With 5 figs. (2 coloured) on 2 plates. [21 refs.]

A useful summary of the pathological changes in the spleen histology of 15 fatal cases of relapsing fever collected in the Gold Coast between 1929 and 1931.

The most important and characteristic change was found to be the occurrence of miliary lesions consisting of a zone of congestion and cell infiltration round the malpighian bodies. These miliary lesions are quite distinct in sections stained with haematoxylin and eosin. When sections were stained by silver methods the spirochaetes were often detected breaking up in these lesions after they had disappeared from the circulation.

The author concludes with a historical survey of the subject and it is pointed out that the miliary lesions of the spleen occurring in the Gold Coast cases correspond with those described by GRIESINGER in 1857 in Egypt in fatal cases of " bilious typhoid " fever, which he believed was a form of relapsing fever. *E. H.*

ROTHERMUNDT (M.) & WICHMANN (F. W.). Studien ueber die chemotherapeutische Beeinflussbarkeit verschiedener Rekurrens-spirochäten (*Spirochaeta crocidurae, Spirochaeta hispanica* und *Spirochaeta duttoni*) bei infizierten weissen Mäusen. [**Studies on the Chemotherapeutic Treatment of Various Relapsing Fever Spirochaetes** (*S. crocidurae, S. hispanica* **and** *S. duttoni*) **in Infected White Mice.**]—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1932. Vol. 77. No. 1/2. pp. 1–12. [10 refs.]

The authors tested the effect of a number of chemotherapeutic substances including arsenic, antimony, bismuth and gold compounds, on mice, infected with three varieties of relapsing fever spirochaetes.

In one series of experiments the blood of the treated mice was examined for six weeks and then the brains tested for any residual infections. In the other series the infected mice were only examined the day following the injection to see whether the spirochaetes had disappeared or not. With all three spirochaetes it was found that very high doses, approaching the *dosis tolerata*, were required in order to cure brain infections and, as shown by a table, even a large proportion of normal mice died after such doses. Even when the brain is negative this may be the result of natural recovery, which is apt to vary with the same strain, for in the past two to four years the percentages of mice showing residual brain infections has fallen from 100 to 22 per cent. in the case of *S. crocidurae*, from 58 to 20 per cent. in *S. hispanica*, and from 100 to 30 per cent. in *S. duttoni*. Consequently it is necessary to employ a large number of animals in using this method of estimating the value of any chemotherapeutic agent. The results of the authors' experiments show that all three infections are equally difficult to cure as judged by the results of examination of the blood or brain. As a general rule, however, *S. duttoni* was more susceptible to arsenobenzol

derivatives and less susceptible to gold compounds than *S. hispanica* and *S. crocidurae*, which gave better results with gold compounds than with the arsenobenzol derivatives.

In all three infections the doses required were so high as to approach the *dosis toxica* and consequently no satisfactory chemotherapeutic index could be obtained. In tests comparing the efficiency of compounds in the treatment of spirochaetal infections it is recommended that strains should be used in which the curative dose does not approach too closely to the *dosis tolerata*. *E. H.*

Dubois (A.). Le traitement par le solganal B en suspension huileuse de l'infection à Sp. duttoni de la souris. [**The Treatment of** *S. duttoni* **in Mice with Oily Suspensions of Solganal B.**]—*Ann. Soc. Belge de Méd. Trop.* 1932. Dec. 30. Vol. 12. No. 4. pp. 429–431.

Seven mice infected with *S. duttoni* each received an injection of 0·005 gm. oleo-solganal, an oily suspension of solganal B. Six of these animals were completely sterilized, including the brains of three of them, and one relapsed. These results suggest that this compound has an activity comparable with solganal B, and is superior in its therapeutic action in this infection to the common trivalent and pentavalent organic arsenical compounds, especially in its action on residual brain infections [see this *Bulletin*, Vol. 29, p. 563]. *E. H.*

Hasskó (A.). Ueber die therapeutische Wirkung von Arsinsäuren und Arsenoverbindungen der Pyridinreihe bei Spirochäteninfektionen. I. Mitteilung: Heilversuche bei der experimentellen Recurrensinfektion (*Spirochaeta crocidurae*) der Maus. [**The Therapeutic Action of Trivalent and Pentavalent Arsenic Compounds of the Pyridin Series on Spirochaetal Infections. Part I. The Treatment of Experimental Relapsing Fever** (*S. crocidurae*) **in Mice.**]—*Zent. f. Bakt.* I. Abt. Orig. 1933. Jan. 30. Vol. 127. No. 4/6. pp. 299–306. [20 refs.]

A table is given showing the therapeutic action of 15 trivalent and 5 pentavalent arsenic compounds belonging to the pyridine series, and one arsenic strychnine compound, on mice infected with the *crocidurae* strain of *S. duttoni*. A number of compounds caused the temporary disappearance of spirochaetes from the blood but only one of them gave results comparable with neosalvarsan treatment. This compound BR 34, the di-sodium salt of 2-pyridone-5-arseno-1′(3′-amino-4′-oxybenzol) had a *dosis tolerata* of 0·005 gm. subcutaneous and 0·002 gm. intravenous per 20 gm. mouse, the *dosis curativa* being 0·001 intravenous. Although the spirochaetes disappeared from the blood and did not relapse, the infection persisted in the brains of the treated mice, as in the case of mice treated with neosalvarsan. *E. H.*

Russell (Helen). **Experimental Relapsing Fever, Accra, 1931.**—*West African Med. Jl.* 1933. Jan. Vol. 6. No. 3. pp. 36–43. With 2 charts. [16 refs.]

The author has made a detailed study of a strain of relapsing fever isolated from a patient in the African Hospital in Accra.

The strain was maintained in the large rat *Cricetomys gambianus* which proved a very convenient host, in which the infection followed

the same course as in monkeys and squirrels. As a rule this strain only produced one attack, but eventually it relapsed and the spirochaetes of the relapse were found to be serologically distinct. When *gambianus* rats infected with this type relapsed, the spirochaetes of the relapse reverted to the original type, there being the usual alternation of two distinct types. It is pointed out that when isolating a strain of the relapse type, results obtained with the first passage animals should be discounted, since in addition to inoculating spirochaetes of the relapse one also inoculates immune bodies against the original type of spirochaetes, and the passive immunity thereby induced is liable to influence the type of spirochaete with which the animal is expected to relapse.

The two types called respectively A and B remained unaltered after passages in *C. gambianus* for many months. In one individual another type (C) appeared on a second relapse, and in addition a fourth distinct type, from which it is concluded that relapsing fever spirochaetes have the capacity of unlimited serological variation. When rats were inoculated simultaneously with spirochaetes belonging to types A and B the resulting attack comprised spirochaetes of both types which could be separated from one another by absorption with immune sera. It was found that the young of infected *C. gambianus* were immune to the type of spirochaete with which the mother was infected shortly before birth, but susceptible to other types. There was no evidence that this inherited immunity is due to infection of the young *in utero* but there was some evidence that the immunity may be acquired from the milk.

C. gambianus were successfully protected for at least six months by vaccination with a mixture of dead spirochaetes and immune serum. Animals inoculated with a Berkefeld filtrate of this mixture did not develop immunity, showing that the antigenic substance was present in the spirochaetes. The immunity to types A and B of the relapsing fever spirochaete seems to be lifelong in *C. gambianus*, for animals were still immune two years after infection ; moreover, removal of the spleen did not seem to have much effect on this active immunity.

Two cases of laboratory infections occurred and both responded to N.A.B. treatment given at the height of the fever. One was infected with the C type spirochaete and two and a half yearslater his serum lysed C type spirochaetes in a 1 : 2 dilution and caused agglutination in a 1 : 320 dilution but had no effect on types A and B. The second boy had a type A infection and a month later his serum lysed A spirochaetes in a 1 : 640 dilution and showed clumping beyond 1 : 5,000 ; it had no effect on types B and C spirochaetes.

Several attempts were made without success to pass living spirochaetes through a Berkefeld N filter. [The author only used pressures of 15 lbs., which other observers have found insufficient to cause the filtration of relapsing fever spirochaetes. Todd and Wolbach (see this *Bulletin*, Vol. 3, p. 404) used a pressure of 50 lbs.] *E. H.*

Beunders (B. J. W.) & van Thiel (P. H.). Untersuchungen ueber die Persistenz von *Spirochaeta duttoni* in Mäusegehirnen bei experimenteller Febris recurrens [**Studies on the Persistence of *S. duttoni* in the Brains of Infected Mice.**]—*Ztschr. f. Hyg. u. Infektionskr.* 1932. Nov. 29. Vol. 114. No. 3. pp. 568–583. With 2 figs. [32 refs.]

Using the Hamburg (1906) strain of *Spirochaeta duttoni* in mice, the authors found that a persistent brain infection was almost a constant

feature, no matter which method of inoculation had been used. The brains of the mice were found to be infective up to 409 days after the original infection, and out of 28 immune mice only two were non-infective (both after an interval of 385 days); therefore this seems to be a characteristic feature of the strain. These results contrast with those of DICKINSON, who in 1932, working with same strain in mice, found persistent brain infections in only one-third of the animals.

With regard to the possibility of an ultra-microscopic stage of the spirochaetes, although this is not excluded, the authors incline to the view that spirochaetes, as such, persist in the brain for the following reasons :—

(*a*) When heated to a temperature of 44°–45°C., which kills the spirochaetes in 30 minutes, the brains of recovered mice lost their virulence at the same temperature as that which killed the spirochaetes in the blood.

(*b*) Spirochaetes are easily overlooked in microscopic examination, especially when rare. Moreover, since it is possible to infect mice by the injection of single organisms and the incubation periods following such inoculations closely approximate those following the injection of infected brain material, it is considered likely that only very few spirochaetes persist in the brain.

(*c*) Spirochaetes were found in sections of the brains of immune mice, stained by Steiner's silver method, and their apparent absence in other silver preparations is attributed partly to their rarity and also to the uncertainty of the staining method. *E. H.*

DELANOË (P.). Une observation d'infection naturelle du chacal due au spirochète marocain, *Sp. hispanicum* variété *marocanum* Nicolle et Anderson 1928, particulièrement longue. [**Natural Infection of the Jackal with** *S. hispanica* **var.** *marocana* **of Particularly Long Duration.**]—*Bull. Soc. Path. Exot.* 1932. Nov. 9. Vol. 25. No. 9. pp. 944–946.

A young wild jackal [presumably caught in the neighbourhood of Mazagan, Morocco] was inoculated with trypanosomes and 24 days later showed spirochaetes in the blood. Groups of 4 guineapigs each inoculated with 2·5 cc. of the blood of this jackal on the 36th and 41st days of the infection all remained negative whilst a group inoculated on the 47th day all became infected. After reinoculation with the blood of one of these guineapigs the jackal's blood was infective up to the 73rd day after the original infection. *E. H.*

KRANTZ (Walther). Ueber die Heilwirkung des Immunserums beim experimentellen Recurrens. [**The Action of Immune Serum in Experimental Relapsing Fever.**]—*Arch. f. Dermat. u. Syph.* 1932. Nov. 21. Vol. 167. No. 1. pp. 136–140.

The serum of a mouse that had recovered 6 weeks previously from an infection with the relapse strain of *S. recurrentis*, was heated to 56°C. for 30 minutes and then mixed with living spirochaetes of the same strain. The resulting mixture was inoculated into mice with negative results. After 30 days these mice were inoculated with the same strain of spirochaetes and all behaved like normal mice.

A series of five mice injected with a mixture of immune serum and spirochaetes kept together for one week, also failed to show any infection with the exception of one individual which was positive for one

day. When inoculated with spirochaetes five weeks later this individual remained negative, one other showed a slight infection and the other three heavy infections. The injection of immune serum at the crisis of the infection not only had no curative effect but seemed if anything to be harmful, for the injected mice died, whilst the untreated ones very rarely died during the first attack. Injections after the crisis had no effect on the course of the infection.

It would seem that only the normal host is capable of responding to an injection of immune serum and spirochaetes in such a way as to protect the animal against infection but even in this case no protection is conferred against subsequent infections. *E. H.*

YUAN-PO (Li). **A New Method for the Cultivation of *Spirochaeta recurrentis*.**—*Kitasato Arch. Experim. Med.* 1933. Jan. Vol. 10. No. 1. pp. 78–86. With 1 plate.

Three strains of *Spirochaeta recurrentis* in Shanghai have been cultivated in a special medium, and kept *in vitro* for 13, 14 and 38 generations without losing their virulence for mice. The culture medium is prepared as follows :—

1 cc. of sterile white of an egg is placed in a test tube and heated to 80–85°C. for about 30 minutes. The white of one egg is sufficient for 15 tubes. The yolk of the egg is placed in a flask containing 400 cc. of sterile 0·8 per cent. saline and thoroughly shaken. The contents of the flask are then allowed to settle for some days in the ice chest. The pH of the supernatant liquid is about 7·0 and it keeps its properties for at least two months. About 5 cc. of this liquid is added to each tube of heated egg white and the resulting medium either used at once or first heated to 55°C. for half an hour. The eggs must be fresh and those whose shells are a dark biscuit colour produce the most favourable culture medium.

One or two drops of citrated infected blood are added to each tube and the medium then covered with sterile paraffin oil and kept at 35–36·5°C. Subcultures are made every 3–5 days by transplanting about 0–5 cc. of a good culture together with a small drop of citrated human or rabbit blood, then covering with paraffin and incubating. The citrated blood is prepared by mixing 2 cc. of blood with 0·2 cc. of a 10 per cent. sodium citrate solution also containing 10 per cent. glucose. The citrated blood keeps for at least 3 weeks if kept in the ice chest.

Some notes are added on the morphology of the spirochaetes observed in the cultures [but the two terminal filaments with small round corpuscles at each end described by the author, and also the figures of them, are very suggestive of degeneration products or artefacts].

E. H.

STYLIANOPOULOS (M.). Transmission expérimentale de la spirochétose des poules au pigeon et au lapin. Persistance du virus dans le cerveau de ces animaux. [**Experimental Transmission of Fowl Spirochaete to Pigeon and Rabbit. Persistence of the Virus in their Brains.**]—*C. R. Soc. Biol.* 1933. Feb. 10. Vol. 112. No. 5. pp. 421–423.

Working in Greece the author found that pigeons of 4 to 5 months, collected from houses free from *Argas reflexus*, the local carrier, when inoculated with the blood of fowls suffering from fowl spirochaetosis invariably became infected, showing fever with the presence of spirochaetes in the circulation. When subinoculated into other pigeons the spirochaetes seemed to have increased in virulence, as 50 per cent.

of the birds succumbed to the infection. Although successive passages in pigeons seemed to increase the virulence for these birds, there was no diminution in its pathogenicity in fowls. The virus was found to persist in the brains of recovered pigeons, in one experiment eight days after the spirochaetes had disappeared from the blood.

Rabbits inoculated intraperitoneally with fowl spirochaetes showed rare parasites in the blood 12–24 hours later which only persisted for about 48 hours. If the spirochaetes were inoculated into the testis, there was a strong local reaction reaching its maximum after 3 to 5 days, and exudate collected from the scrotal sac contained numerous spirochaetes. The brains of recovered rabbits were found to be infective 12 days after spirochaetes had disappeared from other parts of the body. Passage through rabbits had no effect on the virulence of the organism towards fowls. *E. H.*

Mattei. La febbre ricorrente nella Somalia Italiana.—*Ann. di Med. Nav. e Colon.* 1933. Jan.–Feb. 39th Year. Vol. 1. No. 1–2. pp. 49–75. With 5 charts on 2 plates. [15 refs.]

Mochtar (A.). Spirillum cardiopyrogenes.—*Geneesk. Tijdschr. v. Nederl.-Indië.* 1932. Dec. 20. Vol. 72. No. 26. pp. 1754–1758.

Paterson (J. L. H.). A Case of Relapsing Fever with Extreme Anaemia.—*Chinese Med. Jl.* 1932. Sept. Vol. 46. No. 9. pp. 905–907.

RAT-BITE FEVER.

Akasawa (S.). i. Studien ueber die Arzneifestigkeit bei Rattenbisskrankheit, Erreger: *Spirochaeta morsus-muris*. II. Mitteilung: Arsenikfestigkeit. [**Studies on Drug Resistance in Rat-Bite Fever. Part 2. Arsenic Resistance.**]—*Zent. f. Bakt.* I. Abt. Orig. 1932. Nov. 17. Vol. 126. No. 3/4. pp. 261–277.

——. ii. Studien ueber Arznei-Festigkeit bei Rattenbiss-Fieber-Spirochaeten: *Spirochaeta morsus-muris*. I. Wismuth-Festigkeit. **Part I. Bismuth Resistance.**]—*Kitasato Arch. Experim. Med.* 1933. Jan. Vol. 10. No. 1. pp. 57–77. [26 refs.]

i. The author has produced a strain of *Spirillum minus* resistant against neosalvarsan, which was also resistant against other arsenical preparations such as salvarsan, sulpharsenol, villon, silversalvarsan and neostibarsan. This strain has maintained its resistance for two years with 120 passages in mice, and was also resistant when inoculated into rats. When an arsenic resistant strain in mice was treated repeatedly with other therapeutic substances not containing arsenic, the arsenic resistance gradually disappeared; *e.g.*, after ten injections of 0·5 cc. neotrepol, an arsenic resistant strain changed back to the original strain.

In normal mice no difference in virulence was found between the original strain and the arsenic resistant one, but by blocking the reticulo-endothelial system it was found that the latter strain was less virulent than the normal. Compared with the original, the arsenic resistant strain was found to be more susceptible to neotrepol and other compounds not containing arsenic. An arsenic resistant strain was found to be still susceptible to germanin after 10 injections, whilst the

original strain had become resistant after only 5 injections. The arsenic strain, however, was more resistant against combined therapy such as neosalvarsan and germanin, neosalvarsan and neotrepol, than the original strain.

Using parafuchsin as the first preparation and muthanol as the second, in chemotherapeutic interference tests, the mice infected with the arsenic resistant strain reacted in a dilution of 1 : 1,000 whilst mice infected with the original strain reacted in a dilution of 1 : 2,000.

The author states that the spirochaetes of the resistant strain withstand the lytic effects of saponin and taurocholic acid better than the original one.

ii. Mice infected with a strain of *Spirillum minus* were treated by injections of neotrepol and other bismuth compounds such as muthanol and casbis. Little difficulty was encountered in producing bismuth resistant strains which maintained their resistance during 50 passages in mice over a period of two years and also when passaged in rats. When a bismuth resistant strain was treated with neosalvarsan, the resistance disappeared after ten injections. Uncertain results were obtained with germanin and silversalvarsan, whilst trypaflavine and parafuchsin had no effect on the bismuth resistance. No difference in virulence was observed between the normal and drug resistant strains, except in splenectomized mice in which the latter strain was rather more virulent, and in general the properties of the bismuth resistant strain as compared with the normal, agree with those recorded above for arsenic resistant strains. *E. Hindle.*

Burbi (Livio). Spirochetosi spontanea del topo e sodoku sperimentale della cavia. [**Natural Spirochaetosis in the Rat and Experimental Rat-Bite Fever in the Guineapig.**]—*Pathologica.* 1932. Dec. 15. Vol. 24. No. 494. pp. 827–831. English summary.

The author has previously reported in *Pathologica*, 1931, Feb. 15, Vol. 23, No. 472, p. 120, a large number of successes (85 per cent.) from the subcutaneous inoculation into guineapigs of the teeth of wild rats, the animals being killed and the teeth extracted at once.

He has carried out a further series and obtained positive results, the production of rat-bite fever, in all cases with wild rats, but with a rapidly diminishing proportion when the rats were kept in captivity on diet. In one-fourth to one-third of the rats (27·7 per cent.) the blood was infective, the disease being set up by intraperitoneal injection into guineapigs. The author maintains that in *Mus decumanus* there exists a natural spirillosis which can convey sodoku to guineapigs.

H. H. S.

LEPTOSPIROSIS.

Mulder (J.). Over de vroege clinische diagnose van de, aan de ziekte van Weil verwante, sumatraansche leptospira-infecties (Spirochaetosis febrilis). [**On the Early Clinical Diagnosis of the Sumatran Leptospiral Infection Related to Weil's Disease.**]—*Nederl. Tijdschr. v. Geneesk.* 1932. Nov. 5. Vol. 76. No. 45. pp. 5130–5135. [15 refs.] English summary.

In the leptospiroses of Sumatra, although related to Weil's disease in Europe, more than 90 per cent. of the cases do not develop jaundice

and are of a benign character. The most important early clinical symptoms are hyperaemia of the eyeball (episcleral and conjunctival injection) which may be seen under the eyelids in the first days of illness. Next in importance are the muscle pains, especially in the calves of the legs.

Leucocyte cylinders may be found in the urine caused by a cellular exudation in the tubules as a result of the invasion of the kidneys by leptospira. The blood shows a normal or slightly increased leucocyte count, with marked decrease or absence of eosinophiles. Severe cases sometimes show no hyper-leucocytosis. *E. Hindle.*

Slot (Gust A.) & van der Walle (N.). Leptospirosen in Bangkinang en omgeving. [**Leptospirosis in and round Bangkinang (Sumatra).**]—*Geneesk. Tijdschr. v. Nederl.-Indië.* 1932. Nov. 8. Vol. 72. No. 23. pp. 1579–1597. With 6 charts & 1 map. [12 refs.]

At Bangkinang (Middle Sumatra) and its surroundings in 1928–1930, especially during the rainy season, several cases were seen clinically suggesting leptospirosis, mostly in Chinese tin miners. In 17 cases, either by culture, direct or indirect, or by agglutination, this diagnosis was established. With the exception of one case of *L. hebdomadis* infection, the cases were caused by *L. icterogenes* [=*icterohaemorrhagiae*]. By means of dark field examination probable leptospirae were found in water from pools. They were not found in water from the local river (Kampar kanan) or from the mining pits. The water from the pools was either neutral or acid, the river water slightly alkaline. As no leptospirae were found in local rats (*R. diardii*) and the attempts to infect guineapigs and white rats by means of water and mud from the incriminated pools only yielded negative results, the epidemiology of the disease remains obscure. *W. J. Bais.*

i. Petzetakis. L'épidémie d'Hermoupolis de Syra en août 1931 était une spirochétose ictéro-hémorragique. Origine hydrique de l'épidémie. Présence des spirochètes chez les rats d'égout en Grèce. [**The Spirochaetal Nature of the Epidemic at Hermoupolis, Syra, in August, 1931.**]—*Bull. et Mém. Soc. Méd. Hôpit. de Paris.* 1933. Feb. 20. 49th Year. 3rd Ser. No. 5. pp. 201–205.

ii. ——. Nouveau cas de spirochétose ictéro-hémorragique observé à Syra en janvier 1932. Reproduction expérimentale de la maladie sur le cobaye. [**New Case of Spirochaetal Jaundice observed at Syra in January 1932.**]—*Ibid.* pp. 205–209. [13 refs.]

i. See this *Bulletin, ante,* p. 15.

ii. The record of an additional case of Weil's disease at Syra. Spirochaetes were found in the urine and a guineapig inoculated with urine collected on the 13th day of the disease died with typical symptoms of spirochaetal jaundice. *E. H.*

Petzetakis (M.). Sur la sensibilité du campagnol vis-à-vis du virus de la spirochétose ictérohémorragique. [**The Susceptibility of the Field Mouse to the Virus of Spirochaetal Jaundice.**]—*C. R. Soc. Biol.* 1933. Jan. 13. Vol. 112. No. 1. pp. 13–14.

The author inoculated field mice with the Syra strain of *S. icterohaemorrhagiae* and found that they were very susceptible. Large

doses produced a fatal septicaemia and the animals died before jaundice could develop, but when smaller doses were used typical symptoms developed, including jaundice, subcutaneous haemorrhages and the general conditions shown by infected guineapigs. Spirochaetes were found in the kidneys and the infection was reproduced in guineapigs by the inoculation of tissues from these infected field mice.

E. H.

HEGLER (C.). Weilsche Krankheit als Unfallfolge. [**Weil's Disease as an Accident.**]—*Deut. Med. Woch.* 1933. Feb. 24. Vol. 59. No. 8. pp. 298–299.

During the years 1926–1932, 23 cases of Weil's disease have been admitted to the St. George's Hospital, Hamburg, mostly during the bathing season, July to September. Some of these cases must be regarded as accidental occupational infections, such as two men who worked in the drains, a dock labourer working on a dredger in the harbour, and two other cases among the crew of a ship over-run with rats. In the case of the Hamburg dock labourer, who died of the infection, it was necessary to pay compensation.

Last year there were 13 cases of Weil's disease and although the improvements in the serological diagnosis of this infection may partly account for this increase, there also seems to have been a definite rise in the incidence of the disease, and this fact should be borne in mind in considering the question of insurance against occupational liabilities. *E. H.*

MERKLEN (Pr.) & WAITZ (R.). Décharges précoces de spirochètes intracellulaires dans les urines de malades atteints de spirochétose ictéro-hémorragique. [**The Early Discharge of Intracellular Spirochaetes in the Urine of Patients infected with Spirochaetal Jaundice.**]—*Bull. et Mém. Soc. Méd. Hôpit. de Paris.* 1932. Nov. 28. 48th Year. 3rd Ser. No. 29. pp. 1433–1440. With 1 fig.

A record of two cases of Weil's disease in Paris, in both of which spirochaetes were found inside cells, especially mononuclears, in the urine on the eighth day of the disease.

These intracellular spirochaetes were obviously degenerating and when inoculated into guineapigs failed to produce any infection. They were easily detected by simple microscopic examination of fresh specimens, and would seem to furnish a useful method for the early diagnosis of the disease, since they are found several days before free spirochaetes occur in the urine. *E. H.*

KRITSCHEWSKI (I. L.) & KAGAN (N. W.). Ueber das Problem der direkten und indirekten Wirkung in der Chemotherapie. IV. Ueber den Wirkungsmechanismus von Wismut auf Spirochäten. II. Mitteilung. Antwort an Uhlenhuth und Seiffert zu ihren "Bemerkungen zu dem Aufsatz von Kritschewski." Zbl. Bakter. I. Orig. Bd. 118. [**The Problem of Direct and Indirect Action in Chemotherapy. IV. The Mode of Action of Bismuth on Spirochaetes. Part 2.**]—*Zent. f. Bakt.* I. Abt. Orig. 1932. Dec. 23. Vol. 126. No. 7/8. pp. 568–580.

A polemical article in which the authors give records of additional experiments on guineapigs infected with spirochaetal jaundice, treated in various

ways by injections of bismuth yatren A. The authors' conclusions are that in this disease the bismuth compounds act directly on the spirochaetes and kill them without antibodies taking any part in the process. [See this *Bulletin*, Vol. 28, p. 304.] *E. H.*

Thiry (U.) & Tielliu (G.). La spirochétose ictérohémorragique chez la souris blanche. [**Spirochaetal Jaundice in White Mice.**]—*C. R. Soc. Biol.* 1933. Jan. 20. Vol. 112. No. 2. pp. 221–224.

Five lots each of 25 white mice were inoculated subcutaneously with five different strains of *S. icterohaemorrhagiae* pathogenic to guineapigs. In every case the mice became infected, but with three of the strains no clinical symptoms developed, but spirochaetes appeared in the urine after 15 to 30 days and continued there indefinitely. Moreover this urine reproduced the disease in guineapigs.

With another strain the mice became ill on the tenth day and all developed a slight jaundice which lasted two or three days. Three mice died on the 11th day and one on the 12th and ten more in the next two months. All the remaining ones showed spirochaetes in the urine. The infection was transmitted from mouse to guineapig, and guineapig to mouse through four alternating passages. In the case of the fifth strain of *S. icterohaemorrhagiae* the mice became jaundiced after 8 days and five died on this and the following days. The jaundice disappeared after 4 days but 16 more mice died in the next few weeks, and those remaining alive were found to be carriers. Passages from mouse to guineapig and *vice versa* were successful, the urine of an infected mouse producing a fatal infection in the guineapig.

It is evident, therefore, that white mice can be used for the detection of variations in virulence which cannot be recognized in guineapigs.

E. H.

Sardjito (M.). Umwandlung von antigenen Eigenschaften und zugleich Avirulentwerden eines Rattenleptospirastammes durch Züchtung im Wasser. [**Changes in the Antigenic Properties together with Loss in Virulence of Rat Leptospira Strains by culturing in Water.**]—*Zent. f. Bakt.* I. Abt. Orig. 1932. Dec. 15. Vol. 126. No. 5/6. pp. 395–403.

The author has attacked the problem of the relationship of pathogenic strains of leptospira with the common water leptospira, from a somewhat fresh angle and has reached the conclusion that one may change into the other.

The urine of an infected rat, containing pathogenic leptospira, was mixed with sterile Berlin tap water and 2 to 5 days later this material was used for subcultures in various kinds of sterile tap water. Out of 12 kinds of water one from Leiden having a pH of 7·4 was found to give the best growths of leptospira, which grew in company with various contaminating organisms derived from the rat's urine. After five months a pure culture of leptospira was isolated from the water and compared with the original strain. The antiserum against the original rat strain agglutinated the leptospira of the same strain in dilutions of 1 : 12,800, whilst the same antiserum agglutinated the leptospira after water culture only in a dilution of 1 : 100. An antiserum prepared against this water culture strain agglutinated these organisms in a dilution of 1 : 6,400, but had no effect on various pathogenic leptospira including 2 human and 2 rat strains. Moreover,

after water culture the rat leptospira had lost its virulence for guinea-pigs, and in addition was unaffected by oligodynamic factors such as the presence of various metals in the culture media, which are fatal to pathogenic strains.

Cultures made direct from the kidney of a rat infected with the original strain gave no support to the hypothesis that water leptospira might have been mixed with the pathogenic organisms in the kidney, for the resulting cultures contained only organisms of the Weil type.

Consequently the author is of the opinion that the pathogenic leptospira of the rat's kidney can change into the non-pathogenic water type, and therefore one must accept the view that under certain conditions the reverse process may take place and the water leptospira change into the pathogenic type. *E. H.*

VAN THIEL (P. H.). Die Umwandlung von Leptospira pseudoicterogenes, Stamm Leiden. [**Changes in the Leiden Strain of** *Leptospira pseudoicterogenes*.]—*Zent. f. Bakt.* I. Abt. Orig. 1933. Jan. 30. Vol. 127. No. 4/6. pp. 290–298. [26 refs.]

The author has isolated nine strains of *S. biflexa* from various samples of Leiden water in addition to the well-known strain Leiden I. Strains 1 and 4, 5 and 6, 2 and 7, 8 and 9 are identical or very closely related. Strain 3 is related to strains 1 to 7. Strains 8, 9 and 10, are quite distinct from the others. None of the strains are in any way related to the pathogenic Weil strains.

It is of interest that the water strain Leiden I received back from ZUELZER, and also Leiden I supplied by SCHÜFFNER, were quite different from the original strain, Leiden I, kept by the author. Antiserum which agglutinated the latter strain in a dilution of 1 : 10,000 agglutinated Zuelzer's Leiden I only in a dilution of 1 : 100. A water strain after passage through a guineapig, received from ZUELZER, and also a typical Weil strain were also agglutinated only in a dilution of 1 : 10.

As a result of further tests it would seem that both Zuelzer and Schüffner's strains of Leiden I are identical, but differ from the original Leiden I. It seems that this strain must have changed shortly after being received by SCHÜFFNER at Amsterdam, probably under the influence of other culture media.

The author attempted without success to infect guineapigs with strains 2 to 10 of the Leiden water leptospira and also with Zuelzer's strain 2, and is of the opinion that *S. biflexa* (*Leptospira pseudoicterogenes*) is quite distinct from the pathogenic strains. In view of the negative results obtained in attempting to infect guineapigs with these water strains the author considers that it is almost hopeless to continue experiments on the problem of their changing into pathogenic forms.

E. H.

DINGER (J. E.). Duurzaamheid der smetkracht van leptospirenkweeken. [**Duration of Virulence of Leptospira Strains.**]—*Geneesk. Tijdschr. v. Nederl.-Indië.* 1932. Oct. 25. Vol. 72. No. 22. pp. 1511–1519. With 1 plate.

The virulence of pathogenic leptospira strains is maintained for a longer period in NOGUCHI's semisolid agar medium than in VERVOORT's

liquid medium. In the former the leptospirae make a strongly refractive disc constituted by a viscous mass in which the leptospirae are present in extraordinary numbers. This disc is situated at the level of the minimum oxygen tension. The author offers a theory giving an explanation of this curious observation. *W. J. Bais.*

TROPICAL OPHTHALMOLOGY.

A Review of Recent Articles. XIX.*

Trachoma.—Thygeson[1] has reported some of the results of his experiments in inoculating *Macacus rhesus* monkeys with the micro-organism described by Noguchi. Recent cultures of the bacterium obtained from human trachoma induced granular conjunctival changes in four out of five monkeys. These changes closely resembled those found in the early stages of trachoma, but were not followed by pannus and late cicatricial and degenerative developments. The rhesus appeared remarkably resistant to infective matter obtained from human trachoma and its normal conjunctiva differs from that of man in the virtual absence of an adenoid layer. The author considers that the aetiological relationship of the bacterium to trachoma can never be decided by experimental work on monkeys. Trachomatous infection of the monkey's conjunctiva cannot be diagnosed with certainty since insufficient differences exist between the disease induced by inoculation of trachomatous infective matter and that which the animal is liable to contract spontaneously. The disease as it affects Fiji is described by Stuppel.[2] About half the population of 177,000 are Fijians (92,000) whilst East Indians, who number 73,000, form the next largest community. The investigation dealt with the Fijians only, and over twenty per cent. of these are estimated to suffer from trachoma. Incidence is highest in those districts where the hygiene is bad, and clean villages are almost free. The native language has its own name for the disease, and this constitutes an argument that trachoma is not of foreign origin. All types, well-illustrated in the paper by photographs, are met with ; and xerophthalmia with an epidermoid epithelium is not uncommon in old people. The author suggests that the disease may account for the apparent indolence from which the population are sometimes said to suffer. Tiong[3] has compared the effect of acetic acid and chaulmoogra oil in the treatment of sixty-one trachomatous school-children. The type of the disease was follicular and was severe in nineteen cases. He concluded that the two methods of treatment were practically equal as regards efficiency, but that the acetic acid produced more unpleasant effects.

The *Revue Internationale du Trachome* for October 1932 contains a statement by Pages (pp. 167–172) that his experience of the use of chaulmoogra oil in the treatment of trachoma leads him to the conclusion that no specific action can be claimed for the drug ; his colleagues in Morocco, too, hold the same opinion. He suggests that the oil might be used on trial as a prophylactic. C. Trapesontewa of Moscow (pp. 173–179) has conducted some researches on Noguchi's bacterium, and as a result is unconvinced that the micro-organism is the real cause of trachoma. Mme. Delanoë (179–184) argues that

*For the eighteenth of this series see Vol. 29, pp. 855–858.

[1] Thygeson (Phillips). Experimental Granular Conjunctivitis in Monkeys induced by Bacterium Granulosis.—*Amer. Jl. Ophthalm.* 1932. Apr. Vol. 15. No. 4. pp. 293–306. With 9 figs. [19 refs.]

[2] Stuppel (R.). Trachoma in Fiji—an Original Investigation.—*Brit. Jl. Ophthalm.* 1933. Feb. Vol. 17. No. 2. pp. 88–97. With 13 figs.

[3] Tiong (Jose O.). Comparative Treatment of Trachoma with Acetic Acid and Chaulmoogra Oil.—*Jl. Philippine Islands Med. Assoc.* 1932. Oct. Vol. 12. No. 10. pp. 502–506.

trachoma bears pathogenic resemblance to diseases caused by acid fast bacilli such as tubercle and leprosy, and is likely to benefit from treatment appropriate to these diseases. Her arguments, however, are not entirely convincing.

In the issue for January 1933 F. SCHOUSBÖE (pp. 4–20) contributes a paper which deals principally with the diagnosis of the disease in its early stages. There is, unfortunately, no sure laboratory test which will prove the presence of trachoma and one must chiefly rely on clinical observation for a decision. Signs are considered under two headings: the conjunctival and the limbic. A loupe with oblique illumination in a dark room should always be employed. White specks are visible in the very hyperaemic membrane; whitish beads resembling small blisters are also seen in connexion with the vessels or lying between their branches. These beads are tinged with yellow and are translucent; some are yellowish at the centre and translucent at their edges. The membrane is thickened and the course of the blood vessels is irregular; papillae, too, are present. Larger and more translucent sago-like beads are also found. These changes may occur under the age of three years. Limbus changes occur later with vascularization, scalloping of the surface, and, perhaps, the development of sago-like beads. After the age of ten the lesions of the limbus alone may be sufficient to prove the presence of trachoma. RAGANEAU (pp. 33–42) describes the disease as seen in Latakia. He estimates that forty-four per cent. of the general population is infected. Some districts, subject to no exceptional conditions, suffer more than others; the probable explanation is that their inhabitants are more affected by the ravages of malaria, tubercle and syphilis. The arab headdress (Kéfié), usually used as a handkerchief and commonly soiled, is a potent agent in spreading the disease; eye pigments and flies are others. The usual measures are being taken to combat the plague.

Superficial Punctate Keratitis is a disease which deserves some attention owing to the magnitude of the epidemics which have occurred in India, and DOGGART[4] has described cases he has seen in England and exhaustively discussed the various aspects of the condition. He holds with KOBY that the term is applicable to any corneal affection in which the lesion consists of opaque dots involving the epithelium, Bowman's membrane, or the superficial layers of the substantia propria. The clinical picture can be created by a variety of pathological processes. He quotes VERHOEFF'S opinion that keratitis disciformis, acne rosacea keratitis, recurrent corneal abrasion and various other conditions besides that under review possess a common pathology, being types of neuropathic keratitis caused by some shock to the ciliary ganglion or to the Gasserian ganglion. Three types of disease were met with; the most numerous (43 patients) was a non-recurrent superficial keratitis, the main lesions being situated in the anterior layers of the substantia propria. In none of these patients was there any loss of epithelium, though epithelial oedema was invariably present. The disease had no association with any previous illness. One-third of those attacked displayed an impaired sensation of the skin of the eyelids on the affected side. Non-irritating applications proved the most suitable treatment and the duration of the trouble varied from a fortnight to many months. The other varieties had more obvious causes, such as exposure to irritating chemical vapours or

[4] DOGGART (J. H.). Superficial Punctate Keratitis.—*Brit. Jl. Ophthalm.* 1933. Feb. Vol. 17. No. 2. pp. 65–82. With 1 plate & 1 fig. [34 refs.]

fragments of dust, or rosacea, and definite erosion of the epithelium was present.

Xerosis of the cornea.—TASSONI[5] records a peculiar affection of the cornea which he observed in a badly nourished negro aged 30. A band of opacity stretched across each cornea. The band was continuous with a triangular area of thickened conjunctiva near the limbus and occupied the portion of the globe corresponding to the palpebral aperture. The surface appeared to be dried but did not stain with fluorescine. The author regarded the condition as a xerosis due to trophic changes.

Cataract.—GNANADICKAM[6] expresses an opinion in favour of intracapsular extraction and recommends a technique which is based on that of STANCULEANU, TÖRÖK and ELSCHNIG. This technique includes orbicular akinesia, conjunctival suture, blocking of the ciliary ganglion, and a control suture in the superior rectus muscle. The lens is removed in its capsule by gripping the anterior capsular layer in a special forceps ; the lens is dislocated and pressure is then made with a hook on the limbus to aid the delivery by forceps traction. The operation has definite advantages in that it involves less violence to the eye than is sometimes required in Smith's operation and needs no complicated apparatus as in Barraquer's procedure. A complete iridectomy is performed in the majority of cases.

Koman NAYAR and Narayanaswamy NAYUDU[7] have described the technique employed at the Government Ophthalmic Hospital in Madras for the induction of orbicular paresis and iris anaesthesia. WRIGHT devised a method of seventh nerve block by making an injection at the stylomastoid foramen and this was used for some years with satisfactory results. O'Brien's method of injection near the temporo-mandibular joint had, however, been substituted during the past three years as it was found more easy, certain, and safe. A dental syringe fitted with a fine " Alston " needle about 40 mm. long and a solution of four per cent. novocaine to which a few drops of adrenalin have been added are used to induce both the block of the seventh nerve and of the ciliary ganglion. A longer and coarser needle was found liable to induce orbital haemorrhage when used for retrobulbar injection.

Glaucoma.—KIRWAN[8] has contributed a practical paper on non-congestive glaucoma. He emphasizes the three main signs of the disease : (1) Cupping of the optic disc ; (2) increase of intra-ocular pressure ; (3) constrictive changes in the visual field. The increase in pressure is usually variable and may be intermittent. Examination with Bjerrum's screen is recommended and described. He remarks that primary non-congestive glaucoma is a sign of a sick eye in a sick body, some gross sepsis often being present. It is of paramount importance to attend to any septic focus. Elliot's sclero-corneal trephining is the operation which he advocates. The author warns

[5] TASSONI. Xerosis partiel des deux yeux.—*Ann. Soc. Belge de Méd. Trop.* 1932. Oct. 30. Vol. 12. No. 3. pp. 371–373. With 1 fig.

[6] GNANADICKAM (G. Joseph). The Modern Intracapsular Operation for Senile Cataract (According to Stanculeanu-Török-Elschnig Technique).—*Indian Med. Gaz.* 1932. Oct. Vol. 67. No. 10. pp. 559–566. With 5 figs.

[7] NAYAR (Koman K.) & NAYUDU (Narayanaswamy G. J.). Retrobulbar Injections and Seventh Nerve Block.—*Brit. Jl. Ophthalm.* 1933. Apr. Vol. 17. No. 4. pp. 233–235.

[8] KIRWAN (E. W. O'G.). The Diagnosis and Treatment of Non-Congestive Glaucoma.—*Indian Med. Gaz.* 1932. Dec. Vol. 67. No. 12. pp. 661–666. With 1 fig. & 5 charts.

medical men regarding the importance of recognizing the early symptoms of the disease. The same writer has furnished a note[9] on the glaucoma which so often attacks sufferers from *Epidemic Dropsy*. Calcutta has recently suffered from a visitation of this disease. Glaucoma is usually a late complication and appears to bear no relation to the degree of severity of the general disease. The type of glaucoma is entirely non-congestive, though the intra-ocular pressure may be remarkably high. The anterior chamber, too, is either normal or deeper than normal, and the pupil reacts well to light and accommodation. The optic disc is commonly hyperaemic and cupping is only found in the late stages. Field defects are similar to those found in primary chronic glaucoma. The patients complain of haloes round lights and of loss of sight. Pain is absent. The rise in ocular tension is caused by oedema of the ciliary body which is induced by toxic amines found in rice which has been badly stored. Medical treatment is most unsatisfactory and a sclero-corneal trephining should be performed without delay; the results of this operation are excellent. After operation a change of air, if possible, from the endemic area is very advisable.

Ophthalmia Nodosa.—Gabrielidès[10] has recorded a case of caterpillar hair inflammation of the eye. The patient was a man of 60 years who complained of a foreign body having entered his eye when he was cutting a branch from a pine tree on the previous evening. When seen he was suffering from a severe conjunctivitis and keratitis. The discovery of a caterpillar on the patient's hat afforded a clue to the cause of the trouble and an examination with a loupe and slit-lamp revealed the presence of several caterpillar hairs embedded in the conjunctiva and cornea. These hairs are furnished with many little barbs and penetration of the ocular tunics is facilitated by the movements of the eyelids. A channel occupies the centre of the hair, and this contains a poison which is secreted by a unicellular gland; the consequent irritation is thus sufficient to cause a severe keratitis and uveal inflammation with destruction of the eye. When the patient was last seen, three and a-half months after the injury, the eye was quiet and free from discomfort, but three hairs were still lodged in the cornea and the deepest of these rested on Descemet's membrane.

Onchocerciasis.—A most comprehensive account of the ocular complications of onchocerciasis with special reference to the Belgian Congo has been furnished by Hissette[11]. He says that morphologically there is little or no difference between the filarial worm described as *Onchocerca caecutiens* in Central America and that known as *Onchocerca volvulus* in Africa. There is reason to believe that the eye complications which occur during the course of the disease are due to the presence of microfilariae in the ocular tissues. Ablation of the encysted parent worm cuts off the supply of larvae, but is unlikely to help much in other respects. Yet the ablation is often accompanied by an allergic response and this may be beneficial. *Eusimilium damnosum* and

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[9] Kirwan (E. W. O'G.). Epidemic Dropsy Glaucoma.—*Indian Med. Gaz.* 1932. Nov. Vol. 67. No. 11. pp. 636–637.

[10] Gábrielidès (Const. A.). Kératite par poils de chenille.—*Grèce Méd.* 1932. May–Aug. Vol. 31. No. 5–8. pp. 96–104. With 2 figs. [35 refs.]

[11] Hissette (J.). Mémoire sur l'*Onchocerca volvulus* " Leuckart " et ses manifestations oculaires au Congo Belge.—*Ann. Soc. Belge de Méd. Trop.* 1932. Dec. 30. Vol. 12. No. 4. pp. 433–529. With 29 figs. [7 pages of refs.]

Eusimilium noevei were identified by the author as vectors in Africa. It is interesting to find that the connexion between the disease and the midges has long been known to the natives. The eye complications in African onchocerciasis have an insidious onset. The patient complains of some discomfort and conjunctival hyperaemia is found. A very mild iritis unassociated with any keratic precipitates soon sets in, and this is followed by the appearance of small spots of opacity in the cornea. These opacities lie just beneath Bowman's membrane and are confluent in places; they tend to be most numerous at each extremity of the horizontal meridian and to leave an oval clear area with the long axis vertical at the centre of the cornea; this area may remain unaffected for a considerable time. Vascularization of the corneal periphery may occur. General uveitis with degenerative lens changes and phthisis bulbi may follow. Retrobulbar neuritis may also be found. Destruction of the adult worm in its cyst by removal or by injection, and the use of mydriatics constitute the basis of treatment. Diagnosis can be confirmed by excising a small portion of the bulbar conjunctiva and teasing it in normal saline on a warmed slide. The larvae are easily recognized.

Avertin Anaesthesia.—Davis[12] reports favourably on his experiences with avertin anaesthesia in eye operations. He found that the administration of the drug was followed by a fall in the intraocular pressure; and this fall occurred both in glaucomatous eyes and in those whose tension was previously normal. The fall in intraocular pressure seemed to coincide with a fall in blood pressure and to be directly proportionate to the depth of anaesthesia. The avertin was usually given by rectum in a three per cent. dilution with normal salt solution. The dose was 0·1 gm. per kilo of body weight (or 1½ cc. of a three per cent. solution per pound of body weight). A preliminary sedative was ordinarily administered and the customary local anaesthesia employed.

Sleeping Sickness.—Hissette[13] advises practitioners to note the visual acuity of every trypanosomiasis patient before starting a course of treatment. Each eye should be tested separately. The eye complications which affect the anterior segment of the globe, viz., chronic iritis, a diffuse form of interstitial keratitis, conjunctivitis, and oedema of the lids, can be identified without special knowledge; but a recognition of the presence and type of an optic atrophy requires training and experience in diseases of the eye. Optic atrophy may be primary or secondary to a mild neuritis. Dysentery, helminthiasis, and the abuse of tobacco and alcohol predispose to the ocurrence of optic atrophy during treatment and should therefore be eliminated. The author uses tryponarsyl injections, employing the technique of Van den Branden. Most of the cases of complete optic atrophy he has seen had been treated by atoxyl.

Glare.—Livingston[14] has presented a very careful and informative study of the effect of tropical glare upon the eyes of members of the

[12] Davis (Frederick Allison). Tribromethanol (Avertin) as an Anesthetic in Eye Surgery.—*Amer. Jl. Ophthalm.* 1932. Mar. Vol. 15. No. 3. pp. 208–213.

[13] Hissette (J.). Considérations pratiques sur des accidents oculaires de la trypanosomiase ou de son traitement.—*Ann. Soc. Belge de Méd. Trop.* 1932. Dec. 30. Vol. 12. No. 4. pp. 531–538.

[14] Livingston (P. C.). The Study of Sun Glare in Iraq.—*Brit. Jl. Ophthalm.* 1932. Oct. Vol. 16. No. 10. pp. 577–625. With 15 figs., 3 charts & 2 graphs.

Royal Air Force stationed in Iraq. The majority of those who experience the full glare of a hot season show some signs of fatigue or abnormal weakness of the ocular system. Fatigue of accommodation and convergence is almost universal, whilst reduced light sense is exceedingly common. Glare susceptibility does not appear to be affected by the colour of the iris. Light reflected from the ground is specially productive of symptoms such as photophobia, lachrymation, conjunctival hyperaemia with blepharospasm and pupil contraction; lateral rays are also potent in this respect, and glare protectors should be furnished with adequate protection below and at their sides. Crookes' B.1 glass was found generally useful in reducing the light intensity and absorbing the active rays. Very dark glasses have a depressing mental effect. Many of those who are affected by sun glare are highly strung and of a nervous temperament and in treatment the functional element should not be neglected. Any refractive error must be carefully corrected and the patient should not be allowed to mope in a darkened room but should be allowed suitable employment.

Blind and painful eyeballs.—FEJER[15] has again drawn attention to the value of alcohol injections, made in the neighbourhood of the posterior pole of the globe, as a means of enabling a patient to retain a previously painful sightless eye. Primary absolute glaucoma is the chief indication; but it is essential to be quite certain that the glaucoma is not due to a malignant growth. One cc. of a two per cent. solution of novocaine is injected in the orbital tissues surrounding the posterior pole of the eyeball and after the lapse of five minutes one cc. of eighty per cent. alcohol is injected in the same place. The injection is followed by a severe reaction with chemosis and the patient should be treated in hospital.

SAUNDERS[16] has reported on the nature and causes of blindness in the Wa and Tumu districts of the Gold Coast. Onchocerciasis and vitamin deficiency appear to play some part. In Tumu pterygium seemed to be very prevalent and ulceration tended to occur at the apex of the growth. From the particulars given in the paper it is a little difficult to identify some of the diseases which caused blindness; but retino-choroidal troubles probably played some part.

The Annual Report of the Giza Ophthalmic Laboratory is now much more than an annual report of a Government Department and has developed into a valuable scientific periodical. The sixth number opens with an account of the unveiling of a bust of A. F. MACCALLAN—a well deserved tribute to that surgeon's twenty years' work in Egypt during which the system of relief and of research, which has proved so efficacious, was built up by him. Many case reports, well illustrated by pictures, photographs and micro-photographs, are presented. Trachoma is naturally the subject which engages most attention. It is stated that vitamin deficiency is unlikely to bear any specific relation to Egyptian trachoma since keratomalacia is extremely rare in Egypt and the diet of the majority of trachoma patients is fully adequate as regards accessory food factors. All attempts to isolate the *B. granulosis* from cases of Egyptian trachoma have failed hitherto; and

[15] FEJER (Julius). The Treatment of Painful Absolute Glaucoma and Other Eye Diseases with Retrobulbar Injections of Alcohol.—*Amer. Jl. Ophthalm.* 1932. Feb. Vol. 15. No. 2. pp. 135–136.

[16] SAUNDERS (G.). A Report on Blindness in Wa and Tumu Districts, Gold Coast, West Africa.—*Jl. Trop. Med. & Hyg.* 1933. Jan. 2. Vol. 36. No. 1. pp. 5–6.

the Director, R. P. WILSON, therefore visited the United States in order to investigate the characteristics of the disease occurring in America. It is one of the major difficulties presented by the problem that authorities differ in their conceptions of the disease. Trachoma, too, may prove to be a syndrome common to several aetiologically distinct conditions. As regards the American Albuquerque Indians scarring was severe in most cases and was best marked in the retrotarsal folds ; vascularization of the cornea was seldom so extreme as in most Egyptian cases. Some children, however, showed signs which were typical of the early stages of Egyptian trachoma. Trachoma in America principally affects the rural areas and does not spread in the cities. The living conditions of the Indians of the South Western States were found to be almost identical with those of the Egyptian peasant ; purulent ophthalmias, however, are by no means so prevalent.

The Bulletin of the Ophthalmological Society of Egypt for the year 1932 contains the opening address of the President, Dr. M. KHALIL. In it he recounted the measures taken of late years to combat the causes of blindness (especially trachoma) in the country and to ameliorate the lot of those afflicted. The President, too, described the great services rendered by A. F. MACCALLAN in the cause. In a paper on the tattooing of corneal scars A. F. TOBGY drew attention to the importance of denuding the epithelium over the entire surface of the area to be dealt with ; failure to carry the denudation to the periphery results in leaving a white ring round the blackened area. The platinum chloride and hydrazine hydrate method was stated to have proved most satisfactory and to have caused very little reaction. Favourable results in the treatment of Spring Catarrh by the use of injections of splenic extract are reported by M. F. SOROUR. The extracts were prepared from spleens removed for splenomegaly or from fresh spleens obtained from lambs. Trachoma is the subject of several papers. M. A. EL-BAKLY advances the view that the disease may commence in the lower fornix more often than is generally supposed. R. P. WILSON refers to the vascular changes in the end capillary zone of the limbal system of vessels observed by him during slit-lamp examination of trachomatous patients and suggests that these may prove a valuable aid in diagnosis. SOLEIMAN Bey and M. A. H. ATTIAH report that treatment with Ether-benzyl-cinnamique (" Jacobson's solution ") proved ineffective in their hands. The Bulletin, too, contains many interesting case reports by members.

In the new journal, *Folia Ophthalmologica Orientalia*, R. H. ELLIOT (1932. Nov. Vol. 1. Fasc. 1. pp. 26–33. The Special Features of Ophthalmic Practice in Tropical Countries) has most ably discussed the problems which confront the oculist in the Tropics. His summary says : " Tropical Ophthalmology has definite characteristics of its own, due to the habits of the people and to the conditions of climate. The latter strongly influence bacterial, parasitic and insect growth. A sympathetic understanding of the people amongst whom the surgeon works is essential for success. There is a virgin field for the propagation of scientific ophthalmology. Disease conditions little known in Europe are so rampant that any one who will take an interest in the elements of ophthalmology can be of great service to the people and can acquire a skill and knowledge in certain lines of work far beyond that which is possible for his European colleagues. In addition, there is an almost untouched field for scientific investigation along many lines. The essential conditions of success are careful observation,

meticulous notetaking and close analyses of the results obtained. The publication of interesting observations should be encouraged." Regarding trachoma he remarks that it is a label for a large number of different forms of conjunctival disease and emphasizes the importance of early treatment. Max MEYERHOF (pp. 6–25) describes the great progress which has been made in Egypt during the past fifty years in the treatment of eye disease. Real progress began in 1903 when, owing to the generosity of Sir Ernest Cassel, MACCALLAN was enabled to inaugurate the ophthalmic organization which has been so successful in treating the sick and in educating specialists. WILSON (pp. 52–60) contributes a paper on the slit-lamp appearance of the corneal vessels in Egyptian trachoma. FEIGENBAUM (pp. 105–108) publishes notes of a case of anterior lenticonus. He concludes that the condition depends upon a congenital weakness of the anterior layer of the lens capsule which occurs at an early period of embryonic life, but does not itself develop before birth. The Editor, A. FEIGENBAUM, may be heartily congratulated on his periodical, which constitutes a valuable contribution to ophthalmic literature. *H. Kirkpatrick.*

AMOEBIASIS AND DYSENTERY.

Amoebiasis.

Frye (William W.) & Meleney (Henry E.). **Investigations of *Endamoeba histolytica* and Other Intestinal Protozoa in Tennessee: IV. A Study of Flies, Rats, Mice and Some Domestic Animals as Possible Carriers of the Intestinal Protozoa of Man in a Rural Community.**—*Amer. Jl. Hyg.* 1932. Nov. Vol. 16. No. 3. pp. 729–749. With 11 figs. on 2 plates. [41 refs.]

The authors consider that this study indicates that house flies are probably a factor in spread of *E. histolytica* in the community studied, but that none of the animals closely associated with man act as reservoir hosts or assist materially in transmission of *E. histolytica*.

1. From droppings and intestines of house flies caught in homes cysts characteristic of *E. histolytica*, *E. coli*, *Endolimax nana*, and Giardia, were recovered.

2. Faeces from 127 pigs revealed cysts morphologically identified as *E. histolytica* and Giardia each in one animal. Cysts of *E. polecki* and Iodamoeba were very common; while *Endolimax nana* and Chilomastix were found in a few instances.

3. Autopsies on 48 wild rats caught. No evidence of *E. histolytica*. *Endamoeba muris* and *Trichomonas* were frequently found; and one group of rats harboured *Balantidium coli*. *E. muris* from rats was grown in culture and one strain developed typical eight-nucleate cysts.

4. Autopsies on 54 mice caught. No evidence of *E. histolytica*. *E. muris* present in 24 per cent. and the only protozoon found.

5. Faeces from 128 chickens; 18 contained cysts of *E. gallinarum*. No other intestinal protozoon found.

6. Faeces from 22 dogs failed to reveal cysts or motile forms of any intestinal protozoon. *H. M. Hanschell.*

Tallo (Francesco). L'importanza delle verdure consumate allo stato crudo e della frutta nella trasmissione della dissenteria amebica. [**Raw Vegetables and Fruits in Transmission of Amoebic Dysentery.**] —*Riv. Sanitaria Siciliana.* 1932. June 1. Vol. 20. No. 11. pp. 745–8, 751–4, 757–8. [16 refs.] English summary (9 lines).

The author examined by direct microscopy and by animal experiment various samples of vegetables and fruit obtained from the gardens of Palermo or from greengrocers in the town, with a view to determining the presence or absence of infective *E. histolytica*.

In his first tests he used vegetables, washed and unwashed, procured directly from gardeners or herb-vendors. Of 204 samples of various kinds he found 7 with amoebic cysts—3 endives, 2 lettuces, 1 specimen each of fennel and celery. Two endives and one lettuce had been washed when collected by the gardener.

Of 58 samples of fruit obtained from shops or itinerant vendors—30 of figs, 20 of plums, and 8 of strawberries—all but one were negative. The exception was a sample of plums purchased from an itinerant fruitseller.

For animal experiment kittens were employed. Before rectal injection of the material found to be infected, these animals were examined daily for 8 days to prove that they were not passing the amoeba in either vegetative or cystic form. Of the 8 in whom the material was introduced by a rectal tube well up the colon only one

contracted dysentery, dying 20 days later and showing the typical lesions. One other continued to pass cysts, but without presenting symptoms; the remaining 6 continued quite healthy during the succeeding 8 months' observation. The author concludes that the cysts present on these foodstuffs may have little, often no, pathogenicity, and he quotes WALKER & SELLARDS (this *Bulletin*, Vol. 3, p. 63) as recording only 4 cases of dysentery resulting from infection of 20 subjects with cysts of faecal origin, the others passing cysts but presenting no signs of intestinal disturbance. *H. H. S.*

ANDERSON (Hamilton H.). **Amebiasis in Panama and California with Special Reference to Incidence and Treatment.**—*Amer. Jl. Trop. Med.* 1932. Nov. Vol. 12. No. 6. pp. 459–466.

The incidence of amoebiasis in Panama and California was studied, and treatment by carbarsone.

A relatively high incidence of amoebiasis (*E. histolytica*) presumably exists in Guatemala, Costa Rica, and interior of Panama. In Santo Tomas Hospital, Panama City, only 13·9 per cent. of a selected group of patients (from men's medical, women's medical, and obstetrical wards) were found to harbour *E. histolytica*. In recent California surveys, where comparable laboratory methods were used (wet fixed iron-haematoxylin stained smears examined), there has been reported an incidence of 9·8 to 16 per cent. Eighty-eight of the 101 Panama cases of amoebiasis were treated with carbarsone (carbamino-phenylarsonic acid containing 28·8 per cent. arsenic) given orally in average dosage of 5·0 grams in 10 days. The drug was effective without adjuvant in clearing all but one of 37 cases that could be followed during the month of therapy. No evidence of arsenic toxicity was noted when total doses to 300 mgm. per kilogram body weight were given orally. *H. M. H.*

i. PERRY (H. Marrian) & BENSTED (H. J.); ii. BIGGAM (A. G.). **Amoebic Dysentery in Infancy.** [Correspondence.]—*Lancet.* 1932. Dec. 17 & 31. pp. 1358; 1457–1458.

i. To resolve doubts whether amoebic dysentery can occur in infancy [*ante*, p. 22] the authors draw attention to their published records (1929) of laboratory investigation of 500 cases of acute intestinal conditions in children and infants in Egypt. In 73 cases the aetiological agent was *E. histolytica*, and in 80 per cent. of these amoebic cases the age varied from 5 years to 1 year [this *Bulletin*, Vol. 26, p 898].

ii. The author reports from Cairo a case of dysentery in a 3-months-old child. Sigmoidoscopy with a small instrument revealed amoebic ulcers, and motile *E. histolytica* were demonstrated microscopically. Later, autopsy disclosed a solitary amoebic abscess one inch in diameter in the liver, and small amoebic ulcers in the large gut. *H. M. H.*

ANDREWS (Justin) & ATCHLEY (Floyd). **Negative Occult Blood Tests in Carriers of the Dysentery-producing** *Endamoeba histolytica*.—*Jl. Amer. Med. Assoc.* 1932. Oct. 15. Vol. 99. No. 16. pp. 1340–1342. With 1 fig. [21 refs.]

The authors adduce some evidence to show that in their hands the benzidine reaction would recognize the presence of blood in

dilutions up to 1 : 100,000 and on the basis of the results here recorded it seems unlikely that *E. histolytica* is an obligatory tissue parasite.

That it survived within the lumen of the intestine was indicated by the high proportion of amoebic carriers whose stools gave negative tests for occult blood. Thus of thirteen "symptomless carriers" of *E. histolytica* (eleven of whom had simultaneous infections with other protozoa), twelve were apparently free from any bleeding process in the intestine; and of eleven harbouring protozoa other than *E. histolytica*, eight gave negative occult blood tests. Two of the nine cases of *Giardia lamblia* were positive for occult blood; the single case of *Trichomonas* was negative. *H. M. H.*

GRAY (John) & ANDREWS (Mary N.). *Entamoeba histolytica* **and** *Trichomonas hominis* **in Liver Abscess.**—*Chinese Med. Jl.* 1932. Sept. Vol. 46. No. 9. pp. 902–904.

In the chocolate coloured pus aspirated from a liver abscess *Entamoeba histolytica* and *Trichomonas hominis* were found.

The Trichomonas though searched for in the stools was demonstrated there only by culture. The authors note that *T. hominis* was first described in a liver abscess by KESSEL (1925). He found that many of the Trichomonas had ingested red blood cells, which he claimed favoured the view that in certain circumstances *Trichomonas hominis* became pathogenic [this *Bulletin*, Vol. 22, p. 756]. In the present case no ingested red blood cells were seen, and the authors suggest that the Trichomonas travelled into the abscess cavity by way of a bile duct.

They report that in twelve months 1,095 specimens of stools have been examined, and *T. hominis* demonstrated in 28, or 2·5 per cent. Of this total 15, or 1·4 per cent. only were found in direct smears. Sixty-three cultures were made and of these 13, or 19 per cent. were positive. The presence and relative incidence of *Trichomonas hominis* can more surely be determined by cultural methods. The medium used was saline-serum-citrate solution (ANDREWS 1929) in which they grew abundantly. *H. M. H.*

MATTERA (Antonio). Sindromi clorotiche da amebiasi. [**Chlorotic Syndrome in Amoebiasis.**]—*Giorn. Ital. di Malat. Esot. e Trop.* 1933. Feb. 28. Vol. 6. No. 2. pp. 48–50.

Anaemia in amoebic infection is common but usually of secondary type. In this article the author gives brief notes of five patients, in four of whom *E. histolytica* or its cysts were found in the stools.

They presented an anaemia of the chlorotic type, red corpuscles numbering from 3,800,000 to 4,500,000 per cmm., with haemoglobin 60–70 per cent., or C.I. about 0·8; in one patient the Hb. was 55 per cent. and red cells 4,200,000 or C.I. 0·6. Administration of emetine was followed speedily by cure of the anaemia with disappearance of the entamoeba. *H. H. S.*

GREAVES (Aubrey V.). **Perforative Amoebic Ulceration of the Appendix.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1933. Jan. 31. Vol. 26. No. 4. pp. 397–400. With 2 figs. on 1 plate.

The clinical history of this case was unobtainable but the author gives a careful description of the macroscopic and microscopic

findings *post mortem*, and demonstration of the amoebae in the ulcer walls.

He notes that authors have for the most part been unprecise in their reports, basing diagnosis of amoebic perforative ulceration of appendix on clinical grounds without demonstration of the parasite in the tissues. Hogan (1920) described a case in clinical and pathological detail, and demonstrated amoebae in tissues of the appendix.

[In experimental animals a *post mortem* invasion of tissues by *E. histolytica* has been noted.] *H. M. H.*

i. Monnerot-Dumaine (M.). Un signe de l'amibiase intestinale chez l'enfant. [**A Sign of Amoebic Dysentery in the Child.**]—*Bull. Soc. Path. Exot.* 1932. Nov. 9. Vol. 25. No. 9. pp. 947–951. With 2 figs.

ii. Leger (Marcel). Réflexe cutané abdominal chez les dysentériques amibiens. [**Cutaneous Abdominal Reflex in Amoebic Dysentery.**]—*Ibid.* p. 951.

i. This physical sign consists in flexion of the left thigh. It is either spontaneously present—recalling the right thigh flexion in appendicitis—or may be evoked by deep palpation in the left iliac fossa.

ii. In amoebic dysentery patients, the lower abdominal reflex is always more active on the left side than on the right. The middle and upper reflexes are also more marked on the left than on the right side in milder cases of amoebic dysentery. *H. M. H.*

Lee (S. W.). **Carcinoma of the Cervix Uteri Invaded by** *Entamoeba histolytica.*—*Chinese Med. Jl.* 1932. Nov. Vol. 46. No. 11. pp. 1096–1098. With 2 figs. on 1 plate.

Particulars of two cases of carcinoma of the cervix uteri, in which an amoeba was demonstrated in the tissues of the cervix by biopsy. In neither case could *E. histolytica* be found in repeated stool examinations. Neither patient had faecal fistula. *H. M. H.*

i. Acton (Hugh W.) & Chopra (R. N.). **The Treatment of Chronic Intestinal Amoebiasis with the Alkaloids of** *Holarrhena antidysenterica* **(Kurchi).**—*Indian Med. Gaz.* 1933. Jan. Vol. 68. No. 1. pp. 6–12.

ii. Ghosh (Arabinda Bhushan). **A Study on the Preparation of an Efficient Extract of Kurchi** (*Holarrhena antidysenterica*).—*Ibid.* 13–15.

i. A review of 78 cases of intestinal amoebiasis treated with Kurchi bismuthous iodide. Criterion of cure was five, or more, negative stool examinations on different days after cessation of all treatment.

The authors found that alkaloids of *H. antidysenterica* were powerful curative agents in intestinal amoebiasis. In acute amoebic dysentery intramuscular injections of 2 grains daily of the hydrochloride produced a cure as rapidly as emetine, but were very painful. Bismuthous iodide compound of the total alkaloids was an effective remedy in chronic intestinal amoebiasis. Proportion of probable cures to failures was 3·16 : 1, which compared favourably with Knowles' series with emetine bismuth iodide where ratio was 1 : 3·5. The bismuthous iodide compound should be given in doses of 10 grains twice daily preceded by half an hour by a mixture containing one drachm sodium

bicarbonate and 40 grains sodium citrate. No strict dietary measures were necessary unless relapse was very acute.

ii. Dr. Ghosh states that besides the specific action of alkaloids in Kurchi, the tannins, mucilage and resinous matters are presumed to act favourably on dysentery; an alcoholic extract besides containing a reasonable amount of alkaloids should also contain considerable quantities of the above tannins and resinous matters. He found that an extract with 60 per cent. alcohol satisfied all these demands, while 95 per cent. alcohol fulfilled these requirements but entailed a loss of some water-soluble matter. Preference between the two preparations is a subject for investigation by clinicians.

H. M. H.

David (Norman), Johnstone (Herbert) & Stanley (L. L.). **Carbarsone Therapy in Amebiasis.**—*Amer. Jl. Med. Sci.* 1932. Nov. Vol. 184. No. 5. pp. 716–718.

The authors' findings support their conclusion that carbarsone offers a relatively satisfactory, non-toxic, and cheap means of inaugurating therapy in amoebiasis.

It appeared to be quite as effective as emetine, while emetine in clinically effective doses may cause "pathologic damage." Acetarsone and chiniofon have not shown as satisfactory an effect in amoebiasis as has been obtained by carbarsone. The authors found that all but one of a group of amoebiasis cases, observed for 3 or more months, after oral treatment with carbarsone were cleared of *Entamoeba histolytica* (as far as careful stool examinations could reveal), without toxic effect, and without hospitalization. The dosage of carbarsone, 5 gm. in 10 days, may not be enough in severe cases of amoebiasis. Repetition of therapy, supplemented with carbarsone retention enemata, is then indicated. *H. M. H.*

Wight (Toynbee) & Wight (Virginia). **On the Viability of Cysts of *Endamoeba histolytica* under Variable Conditions.**—*Amer. Jl. Trop. Med.* 1932. Sept. Vol. 12. No. 5. pp. 381–386.

The authors claim to have demonstrated as certain that *E. histolytica* cysts under the most variable conditions of temperature, climate, and environment, may remain alive as long as 27 days. Under the most favourable conditions in the ice box at 7°C. a period of 30 to 37 days had been proven possible by Dobell. The authors' own experiments with a strain (N.R.S.) sent by post to them in California by Dobell in London have extended this time to 46 days.

H. M. H.

Dhayagude (R.). Culture de l'*Entamoeba dysenteriae* sur milieux à l'intestin de chat. [**Cultivation of *E. histolytica* on Media including Cat's Intestine.**]—*Ann. Parasit. Humaine et Comparée.* 1932. Nov. 1. Vol. 10. No. 6. pp. 514–519.

A medium containing a small portion of fresh large intestine of cat gave very rich cultures of dysentery amoebae, with development of cysts; these disappeared suddenly after the third or fourth day. A medium containing a small portion of cat's large intestine, heated,

was found very useful for cultivation of dysentery amoebae when horse serum could not be obtained. The media were improved by addition of albumin and starch. *H. M. H.*

MELENEY (Henry E.) & FRYE (William W.). **Infection of Kittens with *Endamoeba histolytica* by Direct Injection of Cultures into the Ileum.**—*Proc. Soc. Experim. Biol. & Med.* 1932. Dec. Vol. 30. No. 3. pp. 277–279.

The authors describe the technique of this surgical procedure. They found that lesions produced in kittens by ileal injection did not differ essentially from those produced by rectal injection, except that in the former lesions involving the ileo-caecal valve and adjacent caecum, and terminal ileum, were more frequent. They believe, as a result of this work, that injection into the ileum is much more reliable than rectal injection as a test for pathogenicity for kittens of *E. histolytica* trophozoites in culture. *H. M. H.*

ANDREWS (Justin). **Cysts of the Dysentery-producing *Endamoeba histolytica* in a Baltimore Dog.**—*Amer. Jl. Trop. Med.* 1932. Sept. Vol. 12. No. 5. pp. 401–404. [16 refs.]

Detailed report of chronic amoebic infection in a Baltimore dog, in whose dejecta cysts were found. The evidence made it probable that the parasite was *E. histolytica*, and that the dog may be in nature an occasional carrier of this parasite, constituting a reservoir of amoebiasis for man and dog. *H. M. H.*

CRAIG (Charles F.). **Observations upon Complement Fixation in Experimental Amebiasis in Dogs.**—*Proc. Soc. Experim. Biol. & Med.* 1932. Dec. Vol. 30. No. 3. pp. 270–272. [11 refs.]

This work was undertaken to throw further light on the phenomenon of complement fixation in amoebiasis. FAUST (1930) had shown that the dog is easily infected with *E. histolytica*, and that the lesions following infection were comparable to those found in intestinal amoebiasis in man [this *Bulletin*, Vol. 28, p. 268].

Alcoholic extracts of cultures of *E. histolytica* were used as antigens. Tests were made upon 29 dogs infected with *E. histolytica*, and in all but one a positive complement fixation reaction developed in the blood serum. Of the infected dogs 22 died and disclosed amoebic ulceration in the colon and in all motile *E. histolytica* in the ulcers. Three dogs killed while still suffering from the infection showed both healed and active lesions, with motile *E. histolytica* in the latter; 2 dogs killed after recovery from infection showed healed ulceration in the colon, and no *E. histolytica* could be found in the gut. *E. histolytica* had been found in the faeces of all 28 infected dogs. The one infected dog giving negative complement fixation serum reaction died 7 days after the colonic inoculation with *E. histolytica* from a very severe amoebic colitis. The time of appearance of the reaction varied between 3 and 14 days after inoculation. Twenty-one dogs gave a 4 + reaction; three, 3 +; two, 2 +; and two, 1 +.

Complement fixation tests upon 42 control dogs free from infection with *E. histolytica* were uniformly negative, and at autopsy these animals showed no evidence of amoebic infection. *H. M. H.*

Paulson (Moses) with the Assistance of Morton Morgenstern. **An Accurate Method for the Numerical Determination of *Endamoeba histolytica* in Vitro and its Possible Use with Other Intestinal Protozoa ; Suggested Clinical Application.**—*Amer. Jl. Trop. Med.* 1932. Sept. Vol. 12. No. 5. pp. 387–399. [11 refs.]

The authors give technical details in support of their claim that by use of a haemocytometer *E. histolytica* can be studied quantitatively in culture under varying conditions. Culture methods can thus be accurately analysed and evaluated.

The liquid portion of the culture is gently and thoroughly mixed by means of a capillary pipette and a drop is placed therefrom on the haemocytometer and the organisms counted as are cells in spinal fluid. The technique applies equally well to *Endolimax nana* and with slight modification to *Trichomonas hominis*. It is probably applicable for quantitative cultural observations of other amoebae, ciliates and flagellates.

Differential tabulation of cysts and trophozoites, as well as of several species of protozoa living together, is also possible by addition of an equal quantity of iodine solution (2 gm. I to 1 gm. KI, in 100 cc. water) to a specific quantity of the material to be examined.

In a human case of acute intestinal *E. histolytica* infection and in an *Endolimax nana* infection occurring in a patient with idiopathic ulcerative colitis, the numerical extent of amoebic involvement before and in association with therapy was determined by securing definite quantities of material through the rectosigmoidoscope, and from freshly voided faeces ; a drop of this material in suspension was placed on the haemocytometer and the amoebae were counted. The authors suggest that this method of study has clinical value. *H. M. H.*

Bacillary Dysentery.

Pergher (J.) & van Riel (J.). La dysenterie bacillaire dans la région des Grands Lacs Africains et la vaccination prophylactique. [**Bacillary Dysentery in the Region of the Great African Lakes, Prophylactic Vaccination.**]—*Bull. Soc. Path. Exot.* 1933. Jan. 11. Vol. 26. No. 1. pp. 46–67. With 1 map. [39 refs.]

A careful study revealing that bacillary dysentery becomes epidemic in this region during the hot rainy season of the year. Shiga bacillus is the chief agent in the outbreak. Prophylactic vaccination with an " anatoxin " (made from formalized strains of Shiga, Hiss and Russell types) of 80,000 individuals was followed by marked reduction of morbidity and mortality. *H. M. H.*

McCay (F. H.). **The Treatment of Bacillary Dysentery by Bacteriophage.**—*Indian Med. Gaz.* 1932. Dec. Vol. 67. No. 12. pp. 666–672. With 1 chart.

A careful essay to evaluate bacteriophage therapy in bacillary dysentery occurring in Calcutta in European and Anglo-Indian patients. Of 231 cases of bacillary dysentery, 111 had bacteriophage given them and 120 had no bacteriophage. The bacteriophage used was a clear amber coloured fluid manufactured by the Government Research Institute at Shillong from a large number of strains of dysentery bacilli, and *in vitro* was potent against all the strains of

dysentery bacilli commonly encountered in Calcutta. The author concludes that bacteriophage treatment is still in its early stages, is well tolerated by bacillary dysentery patients, and in this investigation was successful in effecting speedy cure in 30 per cent. of the cases in which it was used ; but in the remaining 70 per cent. appeared to have little effect clinically. *H. M. H.*

Allodi (A.). Contributo alla conoscenza dell'amebiasi e sua diffusione in Piemonte.—*Giorn. d. R. Accad. Med. di Torino.* 1932. July-Oct. Vol. 95. No. 7–9. pp. 140–150. [16 refs.]

Archer (J. G.). The Increasing Incidence of Amebic Dysentery as a Warning for More Thorough Study of Diarrheas.—*New Orleans Med. & Surg. Jl.* 1932. Dec. Vol. 85. No. 6. pp. 418–421. [11 refs.]

Craig (Charles F.). The Diagnosis and Treatment of Intestinal Amebiasis.—*Southern Med. Jl.* 1932. Dec. Vol. 25. No. 12. pp. 1207–1212.

Garnett (M.) & Sturton (S. D.). *Garcinia mangostana* in the Treatment of Amoebic Dysentery.—*Chinese Med. Jl.* 1932. Oct. Vol. 46. No. 10. pp. 969–973.

Kyu (Kenten). Die Wirkung des Carpains, der Carpainsäure und des Carpainsäureäthylesters auf kultivierte Dysenterie-Amöben.—*Taiwan Igakkai Zasshi (Jl. Med. Assoc. Formosa).* 1932. Nov. Vol. 31. No. 11 (332). [In Japanese. German summary pp. 109–110.]

Merklen (Pr.), Waitz (R.), Albot (G.) & Kabaker (J.). Hépatite amibienne à poussées ictériques répétées pendant onze ans. Abcès du foie consécutif.—*Bull. et Mém. Soc. Méd. Hôpit. de Paris.* 1932. Nov. 14. 48th Year. 3rd Ser. No. 28. pp. 1409–1413.

Yato (M.). Amoebic Dysentery in the Marshall Islands.—*Jl. Oriental Med.* 1932. Dec. Vol. 17. No. 6. pp. 65–69.

TYPHUS AND UNCLASSED FEVERS.

Mooser (Hermann). Essai sur l'histoire naturelle du typhus exanthématique. [**Natural History of Typhus.**]—*Arch. Inst. Pasteur de Tunis.* 1932. July. Vol. 21. No. 1. pp. 1–19. [21 refs.]

Mooser has already shown that the virus of Mexican typhus multiplies in the rat flea and also in cat and dog fleas and in the body louse. The chief difference between the old world and the new world typhus virus, according to Mooser, lies in the different reaction in rats and guineapigs, the old world virus producing an inapparent infection in rats and fever only in guineapigs whereas the new world virus produces fever in rats and fever and scrotal swelling in guineapigs. Mooser points out however that very occasionally scrotal swelling has been noted in guineapigs inoculated with the old world virus (Pinkerton, Sparrow, Nicolle) and also that the virus of Mexican louse-borne typhus may produce fever only, without scrotal swelling, in male guineapigs (Castaneda). The present paper details experiments with a European typhus virus (Tunis) which passed successfully through 3 species of flea, *Xenopsylla cheopis* (rat), *Ctenocephalus canis* (dog) and *Pulex irritans* (human). These fleas were fed on infected rats and then on clean rats or on normal guineapigs: neither the rats nor guineapigs became infected (only a small number of fleas were employed) but when an emulsion of the fleas which had been fed on infected rats was injected into normal male guineapigs these animals reacted and the interesting point was that a considerable number showed a marked swelling of the scrotum. That is to say, the old world virus after passage through the rat and rat-flea produced a similar reaction in guineapigs to that produced by the new world virus. It was noted, however, that this reaction was not permanent; after one or two passages the Tunisian virus ceased to produce swelling of the scrotum in guineapigs. Mooser sums up his paper by saying that the point of capital importance is that prophylaxis of typhus is and remains always the struggle against the louse. This louse menace removed from all peoples, typhus would persist only in the mild endemic form produced by the flea and would no longer endanger humanity.

D. Harvey.

Nicolle (Charles). Origine commune des typhus et des autres fièvres exanthématiques. Leur individualité présente. [**Common Origin of Typhus and other Exanthematous Fevers.**]—*Arch. Inst. Pasteur de Tunis.* 1932. July. Vol. 21. No. 1. pp. 32–42.

This paper is a friendly critique of the paper by Mooser summarized above. Mooser was inclined to the view that the old world virus had been changed into the new world virus by passage through the rat and rat flea and based his assumption on the change produced in the reaction on male guineapigs; Nicolle agrees that the two typhus viruses, old world and new world, and rat virus and human virus, have a common origin but considers the human virus (louse-borne) to be the older. Nicolle considers that Mooser puts too much stress on the reaction produced in guineapigs; after all, as he says, the guineapig is but an intruder in the game and is not naturally involved in the typhus picture as are man, the louse, the rat and rat flea. Nicolle also has noted occasionally (1 per cent.) male guineapigs which when inoculated with epidemic virus give a marked scrotal

reaction. Passage through the rat and rat flea produces a more marked reaction in the guineapig but does *not* change the epidemic virus into the rat virus (endemic).

Nicolle then discusses the question from the viewpoint of the human patient, the rat, the flea, and the louse. Mexican typhus and typhus as seen in Tunis are clinically very much alike, but possibly the Mexican type is less severe although the rash is more profuse and haemorrhages are more frequent. In the rat endemic typhus virus produces a severe fever, often fatal, whereas the epidemic virus produces no fever at all although the blood of the animal is infective and immunity follows. The flea does not suffer although the virus multiplies in the insect and is present for at least 2 weeks or more. In the louse the epidemic virus multiplies in the cells lining the intestine and the excreta become infective about the ninth day; the insects die about the 21st day. On the other hand the endemic virus multiplies much more rapidly in the louse and kills them as early as the 5th day. Nicolle is of opinion that this difference in the action of the two viruses in the louse has an important bearing on the transmission of the rat typhus virus by the louse. Also as the rat does not die of epidemic typhus, the flea does not necessarily leave the rat and therefore does not attack man.

It is on the difference in the action on rats that Nicolle bases his assumption that the epidemic virus is the older virus, the rat having become tolerant to this infection but susceptible to the endemic virus.

D. H.

Kodama (Makoto). **On the Classification of Typhus in its Epidemiological, Clinical and Etiological Observations.**—*Kitasato Arch. Experim. Med.* 1932. Oct. Vol. 9. No. 4. pp. 357–361.

This attempt to classify typhus fevers is rather likely to confuse matters further, as the writer employs the term "eruptive fever" to describe endemic typhus or Brill's disease. This is unfortunate, since this term has already been used to designate the disease met with in Marseilles and North Africa, and known as fièvre boutonneuse. The author suggests that the virus of endemic typhus or Brill's disease is the original virus and that typhus was a disease of rats only, rarely conveyed to man by the rat flea, but at one time or other this virus established itself in man and the body louse and gave rise to typhus in its epidemic form. *D. H.*

Fialho (Amadeu). Tifo exantematico de São Paulo. [**Typhus in S. Paulo.**]—*Rev. Med.-Cirurg. do Brasil.* 1932. July. Vol. 40. No. 7. pp. 183–205. With 11 figs. on 6 plates. English summary (2 pages). [Summary appears also in *Bulletin of Hygiene.*]

Though designated "typhus," the condition depicted would appear to be a newly described entity or a marked variation from recognized forms of typhus and typhus-like diseases. Hence the following account must be somewhat full.

In 1929 certain cases were observed in S. Paulo which ran a febrile course with a rash and a typhoid state and in many terminated fatally. Inquiry showed that between 1924 and 1927 there had been seen about one case annually, but in 1929 an extensive outbreak of at least 70 cases occurred; in November 1930 to January 1931, 16 cases; in

October 1931 to February 1932, 21, that is, it was a disease prevailing in, if not limited to, the hot season. As regards sex the distribution was equal; in the first 61 there were 31 males, 30 females nearly all adults, but in the district involved in the general population females preponderated, 3 : 2. Most of the patients were Brazilians, though other races, even Europeans, did not escape; no evidence could be obtained that infection had been imported.

The clinical evolution is interesting and is given in detail in order that comparison may be made with other typhus-like diseases. Onset is abrupt, with headache, shivering and fever; bilious vomiting is frequent and in the earlier cases epistaxis, but this was less common in the later. Myalgia was intense, pressure causing acute pain; stupor set in fairly early. The conjunctiva was injected and on the 4th or 5th day the face and limbs were swollen and appeared shiny in all severe cases and at the end of a week the typhoid state was complete. There might be bleeding from the gums; the bilious vomiting usually ceased in the first week, but occasionally persisted with haematemesis. The temperature rose to 40–42°C., then in 2 or 3 days showed a deceptive fall to rise again before the fatal termination; the pulse, at first strong, soon became weak and rapid (120). If the patient recovered, the temperature usually came down by lysis between the second and third weeks.

The rash, at first roseolar, later petechial and often confluent, appeared regularly on the third day, first on the legs, then involving the whole body including the face and palms. It might also be seen in the mouth and larynx and trachea. Bronchitis was common, and the sputum at times haemorrhagic. The liver rarely showed any enlargement but splenomegaly was constant (to twice the normal); there was albuminuria and, if there were jaundice, bile pigments in the urine. Delirium usually set in on the 3rd or 4th day; in some the cerebrospinal fluid was under pressure, but showed no other change. The fatality rate was between 70 and 80 per cent. and just over half of these deaths (52·2 per cent.) occurred in the first week.

No organism could be cultivated from the blood either aerobically or anaerobically; the blood was, however, pathogenic (see later) not only during the attack but after death; a citrated sample kept in the ice-chest was virulent after 10 days. The Weil-Felix reaction with Proteus X19 and X2 was variable, in some only in a dilution of 1 : 50, in others up to 1 : 6,400.

The *post-mortem* findings need not be detailed minutely; they can be inferred from the clinical symptoms—congested lungs, petechial rash, cutaneous haemorrhages, and, as would be expected, petechiae on the serosae; the spleen is dark and swollen.

Animal inoculations were made into guineapigs and *M. rhesus* with positive results, symptoms and *post-mortem* findings being similar to those in man. Of the blood 2 cc. citrated was the dose injected, or if brain emulsion was used 2 cc. of an emulsion of 1 gm. in 10 cc. physiological saline. The scrotal reaction was fairly constant and Rickettsia were seen in the peritoneum and in Descemet's membrane and in the testicular lesions. The fatality in animals was 70 per cent., higher, that is, than in yellow fever. Rabbits were also inoculated but these animals, strange to say, reacted mildly, the infection in them running a benign course.

The vector has not so far been determined; experimentally, *Amblyomma cajennense* and *Ornithodorus rostratus* conveyed infection;

lice, which were very rare, did not. A list of 5 urban insect parasites and 14 suburban and rural is given, none of which has so far been incriminated, but further study of these will doubtless be undertaken, as all the evidence points to some ectoparasite of some rustic animal.

The disease does not coincide with either of the three main types of typhus—the European, the Mexican, or the Rocky Mountain spotted fever—but rather occupies a position intermediate between the last two. Studies and experimental work on cross-immunity would also probably help greatly in elucidating this interesting infection. *H. H. S.*

KOUWENAAR (W.), SNIJDERS (E. P.) & WOLFF (J. W.). Onderzoekingen over mijtekoorts. [**Mite Fever.**]—*Nederl. Tijdschr. v. Geneesk.* 1932. Oct. 1 & 8. Vol. 76. Nos. 40 & 41. pp. 4640–4647; 4746–4757. With 11 figs. (5 on 1 plate). [50 refs.] English summary.

I. *Introduction.*—Mite fever is an acute, non-contagious, infectious disease with a typhoid-like course, which was described under the name pseudotyphus of Deli by SCHÜFFNER and WACHSMUTH in 1908 as endemic on the east coast of Sumatra. Its most characteristic appearances are the primary lesion, a necrotic ulcer, with swollen regional glands and it is transmitted through the bite of the larva of the mite *Trombicula deliensis*. The best known of these mite diseases is the Kedani or Tsutsugamushi disease, in which, however, leucopenia and a mortality of 40 to 60 per cent. were prominent characters, whereas in the Sumatran form leucopenia was observed in only 10 per cent. of the cases and the mortality was about 5 per cent. That the Weil-Felix reaction was negative in the Japanese form was probably due to the test having been applied with Proteus X19 which is the strain used for the diagnosis of true typhus. It was found that in the Sumatran disease a positive O-agglutination was demonstrable not to X19 but to the anindologenic Proteus X-Kingsbury strain. Cases have been described also in Annam, Saigon, Malaya, Java and New Guinea. The African form, described from S. Africa and Kenya, is a tick fever in which serum agglutination is obtained with X19, X2 and X-Kingsbury. A disease which is common on the east coast of Sumatra, "tropical typhus" (FLETCHER), has a great deal in common with mite fever—clinical course, exanthem, epidemiology and Weil reaction. Of the two forms of "tropical typhus"—shop typhus (X19 agglutination) and scrub typhus (X-Kingsbury agglutination)—it is the latter which more closely resembles mite fever in its epidemiology. The organism, claimed to be causative, of tsutsugamushi disease has been variously named *Rickettsia nipponica* and *Rickettsia tsutsugamushi*. NAGAYO implanted infective material in the anterior chamber of the eye in rabbits, guineapigs and monkeys. He obtained on and in Descemet's membrane an abundant culture of rickettsiae. He and his co-workers named the organism *Rickettsia orientalis* and claimed that it was the virus of tsutsugamushi. It seems probable that mite fever is also a rickettsia infection. These conclusions, however, may have to be held in abeyance with the discovery that, after intraperitoneal inoculation of guineapigs and white rats with normal guineapig brain emulsion, smear preparations from the peritoneum or the tunica vaginalis showed bodies indistinguishable from rickettsia.

II. *Experiments on Monkeys.*—The Japanese observers found that subcutaneous inoculation of the blood of a tsutsugamushi patient in *Pithecus fuscatus* was followed by a typical primary lesion, fever, buboes and leucopenia with rickettsiae in the histiocyte cell elements of the organs. Intracutaneous inoculation gave even better results. The authors of this paper adopted for the most part the intracutaneous method and their test animals were macaci—24 rhesus, 15 cynomologus and 7 nemestrinus. Of these 28 showed definite symptoms. A papular lesion, developing after 8 to 9 days, was the most conspicuous effect. This was distinct from any local reaction of inoculation, which had usually disappeared in 5 days. Swelling of regional glands took place but rise of temperature was definite in only 3 cases. Other general symptoms also were slight in comparison with local effect. Leucopenia with lymphocytosis was evident more particularly in those animals in which the primary lesion was well developed. An examination of the blood of the infected animals was repeatedly made for agglutinins to both H and O-variants of Proteus X19 and Proteus X-Kingsbury. No agglutination was ever obtained to X19. It was found that even before infection an agglutination of 1/25 to 1/50 could be obtained to the O-X Kingsbury strain and positive readings were therefore only recorded when the values after infection were higher than the initial values. The titres, obtained in 16 cases, to this strain were never very high. Cultures of blood and organs from the test animals were usually sterile and never yielded a Proteus-like or other specific organism. Examination of smears and sections for rickettsia-like bodies was difficult and unsatisfactory but they were found five times in the test monkeys at the height of the infection. The general conclusion of the experimental research is that the possibility of producing a localized and slight infection with the virus of mite fever was demonstrated but that evidently the investigation required the use of the species *Pithecus fuscatus* before it could be considered sufficiently striking. *W. F. Harvey.*

Wolff (J. W.) & Kouwenaar (W.). Onderzoekingen over mijtekoorts. [**Mite Fever.**]—*Nederl. Tijdschr. v. Geneesk.* 1933. Jan. 21. Vol. 77. No. 3. pp. 269–280. With 8 figs. (6 on 3 plates). [Refs. in footnotes.] English summary.

This, the third part of the work done on identification of Sumatran mite fever with the Japanese tsutsugamushi (Kedani) disease, contains the experiments on rabbits in place of monkeys.

III. *Experiments in Rabbits.*—Citrated blood of a patient suffering from Sumatran mite fever, taken on one of the first days of fever, was used. It was injected into the testicle and further serial injection practised 7 to 9 days after. For this the infected testicle was sterilely removed and smears and sections made. A suspension of triturated tunica vaginalis and testicle in normal salt solution was used in a dose of 0·2 to 0·5 cc. to inoculate the testicle of a fresh rabbit and so on in series. These tests have demonstrated that it is possible to produce specific changes in rabbits' testicles. An orchitis with mononuclear phagocytic infiltration develops in both tunica vaginalis and testicle and in these mononuclear cells rickettsia-like inclusions are found. The changes are very like those described for the infection with the virus of tsutsugamushi (kedani) disease of Japan, while the inclusion bodies are morphologically like the rickettsiae of the various

typhus-group diseases. In the experiments here performed the changes observed were less constant than in tsutsugamushi, where the virulence increases by rabbit passage. Just as in the case of the monkeys used in previous experimentation a certain variability in the outcome of the animal tests was apparent. In a certain number of cases it was possible to reproduce in monkeys by intracutaneous inoculation of testicular suspension the typical primary lesion already described. *W. F. Harvey.*

Marçon & Audoye. Au sujet de quelques cas de typhus endémique observés à bord du cuirassé *Paris.* [**Cases of Endemic Typhus on Board a Cruiser.**]—*Bull. Soc. Path. Exot.* 1932. May 11. Vol. 25. No. 5. pp. 390–396.

In 1931 there were a few mild cases of endemic typhus on board the cruiser "Paris," but in December of that year and in January 1932 there were 9 cases of severe typhus; all recovered but high fever, delirium and great prostration was noted in two cases at least. This small epidemic was investigated by the authors. Forty rats were collected on board and sent to the laboratory and the virus of typhus was isolated from them. It was noted that the outbreak occurred at the coldest time of the year which is contrary to the usual experience. The authors are of the opinion that infection took place during the night when the men were sleeping in the 'tween decks in hammocks; they found that the rats ran along the steam pipes under the decks and frequently jumped down on to the hammocks and from hammock to hammock. Rats' nests were found below these pipes and the electric cables; in such a situation a suitable temperature is available all the year round for the multiplication of fleas and the development of the virus and there is a close association between the rats and the sleeping men. *D. H.*

Tonking (H. D.). **Preliminary Observations on the Etiology of Kenya Typhus.**—*East African Med. Jl.* formerly *Kenya & East African Med. Jl.* 1932. Sept. Vol. 9. No. 6. pp. 152–159. [11 refs.]

In Kenya Colony for the last fifteen years a form of mild typhus has been recognized but little experimental work has been done and, although it has been shown that the Weil-Felix reaction is positive, Rickettsia have not so far been demonstrated. The author utilizing as inoculum the emulsion of an excised primary ulcer succeeded in establishing the virus in guineapigs. The reaction produced was similar to that following the inoculation of endemic typhus virus or Mexican typhus virus, *i.e.*, fever and severe testicular reaction and in smears made from the tunica vaginalis of the experimental animals the author was able to demonstrate by means of Giemsa stain large numbers of Rickettsia.

The virus was passed in series through a number of generations and *post mortem* it was possible to demonstrate changes in the brain and other tissues similar to those described by Wolbach, Mooser and others. Both in the sections of the brain and tunica it was possible to demonstrate Rickettsia-like bodies in suitably stained preparations.

The vector in East Africa is not yet known but it has been noted that in the season when most cases occur just after the rains the "grass" rats are driven into the houses and this suggests that some ectoparasite of the rat is concerned. *D. H.*

Ross (G. R.). **Eruptive Fevers of the Typhus Group, with Notes on a Fever of the Group observed in Southern Rhodesia.**—*South African Med. Jl.* 1932. July 23. Vol. 6. No. 14. pp. 453–459. With 5 charts & 1 fig. [26 refs.]

An historical review of the group of typhus-like diseases is given and fourteen cases of an exanthematic fever in Southern Rhodesia are described. The cases occurred during the summer and autumn months during the period of the rains. Twelve of the patients were resident in the town of Salisbury, two on farms in the neighbourhood. No connexion could be traced between them although four were troopers in B.S.A. Police and one was a sergeant in the charge of their hospital.

The clinical symptoms were typical of the typhus group of fevers with mental symptoms in severe cases and a profuse maculo-papular rash in all which involved as a rule the palms and soles. In the later cases of the series a very definite tache noire or primary ulcer was quite definitely present. The patients described this as " the bite " but none had observed the insect responsible.

Laboratory investigations.—Although the Weil-Felix reaction was carefully studied, using both indologenic and non-indologenic strains of Proteus no significant positive reaction could be demonstrated. The sera were tested in some cases up to six weeks after discharge from hospital.

Guineapigs inoculated with blood from patients taken during the early stage of the disease did not react. Although no insect vector could be definitely incriminated there was association in all cases with tick-infested dogs. *D. H.*

Wicht (J. F.). **Endemic Typhus in Cape Town.**—*South African Med. Jl.* 1932. July 9. Vol. 6. No. 13. pp. 443–446.

Wicht describes 10 cases of endemic typhus which have occurred in Cape Town in the last 5 years. All were Europeans and free of lice. The Weil-Felix reaction was positive. He discusses the nomenclature of the disease and proposes that such cases should be designated " paratyphus " ; he suggests the possibility of the virus of this type of fever being picked up by lice and transmitted in epidemic form.

D. H.

Lépine (P.). Résultats éloignés de l'immunité croisée des cobayes aux diverses souches des typhus exanthématiques humain et murin. [**Results of Crossed Immunity of Guineapigs to Strains of Murine and Human Typhus.**]—*C. R. Soc. Biol.* 1932. Vol. 111. No. 40. pp. 931–933.

As already noted, the author has shown that guineapigs which have reacted to typhus rat virus and recovered are immune to the human virus but this immunity is transitory, whereas guineapigs which have reacted to the human virus and recovered are immune to the rat virus and remain so. Guineapigs which are immune to the rat virus are also immune to the human endemic virus but may not be immune to rat virus of other towns or localities.

The author has extended this work and now finds that there are two groups of rat typhus virus, the one virulent, the other little

virulent ; the former a good antigen, the latter not ; the former produces a good and lasting immunity in guineapigs, the latter does not ; and if a virus of Group I is employed in cross immunity experiments no differences can be made out between the human endemic and epidemic or rat virus. *D. H.*

Nicolle (Charles), Laigret (J.), Marcandier & Pirot (R.). Le rat, animal réactif des typhus endémiques bénins. Longue conservation de leurs virus chez le rat. [**The Rat as Test Animal for Benign Endemic Typhus.**]—*C. R. Acad. Sci.* 1932. May 17. Vol. 194. No. 20. pp. 1704–1706.

In this research the authors employed 3 typhus viruses ; 1. African typhus, old world epidemic ; 2. endemic typhus of ships ; 3. Mexican typhus (Mooser). Old world typhus produced in rats an inapparent infection, no fever or other symptoms but the blood and brain were infective for guineapigs. The Mexican virus and the virus of ship typhus produced fever and swelling of the scrotum in rats and many of the infected animals died. It was also shown that the brain of rats which recovered was still infective up to 37 days and that of guineapigs up to 40 days after inoculation ; thus explaining how readily the virus of endemic typhus may be isolated from wild rats even in the non-endemic areas. *D. H.*

Reimann (Hobart A.), Ulrich (Henry L.) & Fisher (Luther C.). **Differential Diagnosis between Typhus and Spotted Fever : Report of a Case and the Isolation of a New Mild Type of Spotted Fever Virus.**—*Jl. Amer. Med. Assoc.* 1932. May 28. Vol. 98. No. 22. pp. 1875–1879. With 5 text figs. [10 refs.]

Scattered cases of Rocky Mountain spotted fever have now been noted in areas far removed from the original region of its discovery and may be met with at the same time and in the same place as typhus. It is noted that typhus (old world) occurs usually in the winter, Brill's disease, endemic typhus, in the summer and autumn, and spotted fever in the spring and summer. The first named disease is transmitted by lice, the second by the rat flea and the last by a tick—but the only definite method of differentiation is by means of crossed immunity experiments. The authors describe a severe case of fever which on clinical grounds was diagnosed as typhus fever. The titre of the Weil-Felix reaction was 1–1,280 on the 24th day. It was discovered later that the man had been bitten by wood ticks 14 days before he developed fever. Two guineapigs were inoculated with blood taken on the 12th day of the fever and one reacted ; from this others were inoculated and a strain of virus (Minnesota) was established. None of the animals died and only about 50 per cent. of the males showed a testicular reaction. Animals recovered from infection with the Minnesota strain were immune to Eastern spotted fever virus but not to the virus of endemic typhus. *D. H.*

Gasser (R. R.). **Rocky Mountain Spotted Fever (Eastern Type). Report of Case.**—*U.S. Nav. Med. Bull.* 1932. Oct. Vol. 30. No. 4. pp. 513–516.

It has recently been shown that a mild type of Rocky Mountain spotted fever occurs in the eastern States of North America as well

as or along with endemic typhus or Brill's disease. [This is another instance of the difficulties arising from " place names " for diseases ; we now have Malta fever occurring in the Rocky Mountains and Rocky Mountain fever in Marseilles.] The author describes a case which he met with in Maryland in a young naval officer. There was a profuse macular rash involving the arms, thighs, back, palms and soles. The Weil-Felix reaction was positive and there was a history of tick bite about ten days before onset of the fever. The predominant species of tick in the focal areas is *Dermacentor variabilis*. *D. H.*

Nicolle (Charles). Sur une menace constante d'erreur dans l'étude comparative des virus des fièvres exanthématiques. Portée critique de cette menace. [**Source of Error in Comparative Study of Typhus Viruses.**]—*Arch. Inst. Pasteur de Tunis*. 1932. July. Vol. 21. No. 1. pp. 20–24.

Nicolle points out that in the summer in places such as Tunis rat, dog, cat and human fleas are exceedingly prevalent and it is practically impossible to prevent research workers or experimental animals being bitten. That this is so may account for some contradictory results obtained by workers in research on rat typhus virus. Special precautions should be taken by anyone who intends to undertake such work. All workers should be protected by 3 doses of Weigl's vaccine [see Nicolle & Sparrow below]. The work should be carried out in the cold weather when fleas are scarce, as few experimental animals as possible should be used and they should be specially housed.

D. H.

Biggam (J.). **Three Cases of " Tropical Typhus " occurring in Bangalore, India.**—*Jl. Roy. Army Med. Corps*. 1932. Aug. Vol. 59. No. 2. pp. 96–109. With 3 charts. [25 refs.]

The author gives a historical account of the typhus-like fevers which have been described in various countries ; referring, as is only right in the Royal Army Medical Corps journal, specially to the pioneer work of McNaught in South Africa in the years 1907–11 on a typhus-like disease which he definitely distinguished from enteric fever and identified with Brill's disease. It is of interest to note that at that time, 1910, the suggestion was put forward that this fever was due to tick bite.

The present paper is concerned with 3 cases of typhus-like fever which occurred in Bangalore in 1931. The fever lasted 16 days ; the temperature soon reached 105°F., was then remittent from about 102° to 100° for ten days, and fell to normal by lysis on the 18th day. The pulse was relatively slow throughout. The rash was first noted on the 4th day, at first macular then papular. The palms and soles were involved. It became petechial on the 13th day and began to fade on the 19th, staining being visible 10 days after the temperature had reached normal.

The Weil-Felix reaction was negative in Case I ; 3 tests were made, the last on the 18th day of disease.

Case II was negative on 7th day, 12th day positive XK type 1/125, X19 type 1/50.

Case III	7th day XK	negative.
	X19	,,
	10th day XK	1/250
	X19	1/250
	17th day XK	1/50
	X19	negative
	24th day	all negative.

Blood cultures were sterile in all 3 cases. All had been inoculated with T.A.B. vaccine and a sympathetic rise of the typhosus and paratyphosus agglutinins was noted. There was no history of tick bite in any. *D. H.*

KUNDU (M. L.). **A Case of Typhus Fever in Rangoon.**—*Indian Med. Gaz.* 1932. July. Vol. 67. No. 7. p. 390. With 1 graph.

A case of severe fever with delirium, rapid pulse, typhus-like rash and marked leucocytosis. Weil-Felix reaction positive in a dilution of 1–2,000. The patient was a clerk living under good sanitary conditions; no lice could be found on him or in his house and there was no history of tick-bite. [Nothing is said as regards rats or rat fleas.] No other cases have been reported. *D. H.*

CHRISTIAN (C. R.). **A Case of Typhus due to Tick Bite.**—*Jl. Roy. Army Med. Corps.* 1932. Dec. Vol. 59. No. 6. pp. 445–448. With 1 chart.

HEPPLE (R. A.). **Notes on the Laboratory Investigation of the Case.**—*Ibid.* pp. 448–450.

The patient stated that 5 days before fever commenced she had removed from the skin of the groin a reddish brown tick, not further identified. On admission to hospital at Delhi 5 days later a profuse maculopapular rash was present with injection of the conjunctiva and swelling of the inguinal glands close to the tick bite. The fever lasted about 14 days. The Weil-Felix reaction on the 8th day of the fever was OXK 1/125, OX19 nil; 23rd day, OXK 1/50, OX19 1/25. A guineapig inoculated with 3 cc. of blood taken on the 8th day of the disease showed no definite reaction either febrile or by swelling of the testicle, but had an inapparent infection since other animals inoculated from it developed fever and showed slight increase of the Weil-Felix reaction as compared with normal animals.

D. H.

FLETCHER (William). **Tropical Typhus.**—*Brit. Med. Jl.* 1932. Dec. 24. pp. 1140–1141.

A paper read in the Section of Tropical Medicine at the Centenary Meeting of the British Medical Association in London in 1932. A resumé of our present knowledge regarding tropical typhus.

The symptoms are those of mild typhus; the vascular lesions of true typhus have been shown to be present and Rickettsia have been demonstrated in the tissues of cases. Also the Pinkerton-Mooser reaction has been noted in inoculated guineapigs. The Weil-Felix reaction was also discussed; a positive reaction has been obtained in rats and rabbits inoculated with the virus. *D. H.*

Souchard, Marneffe, Lieou & Vielle (E.). Un cas de fièvre fluviale du Japon, observé en Cochinchine ; étude clinique et expérimentale. [**Case of Japanese River Fever in Cochin China.**]—*Arch. Insts. Pasteur d'Indochine.* 1932. Apr. No. 15. pp. 97–151. With 57 charts & 6 plates. [24 refs.]

*The first case of tsutsugamushi fever in Cochin China (1929) is described in detail. Clinically there was no difference from the disease as it occurs in Japan and elsewhere, but it was noted that when the virus was inoculated into guineapigs it produced a severe reaction and the animals generally died, whereas the Japanese virus only produces a mild reaction (often inapparent) in guineapigs and the animals do not die. In monkeys the Cochin China virus produces a typical sore and fever reaction identical with that caused by the Japanese virus. *D. H.*

Durand (Paul). Essais de sérothérapie curative du typhus exanthématique par voie méningée. [**Serotherapy of Typhus by the Meningeal Route.**]—*C. R. Acad. Sci.* 1932. May 17. Vol. 194. No. 20. pp. 1764–1766. With 1 chart in text.

The author treated 14 cases of typhus fever by means of intrathecal dosage of convalescent serum. A single dose of 25 cc. of serum was given. Temperature charts are shown and in two cases the temperature dropped to normal 24 hours after the injection. In 7 cases the temperature dropped several degrees and remained at this lower level and the fever followed a mild course. The author claims that this method of treatment shows curative properties and should be employed whenever possible in typhus fever and in allied diseases. *D. H.*

Zinsser (Hans) & Castaneda (M. Ruiz). **Studies on Typhus Fever. IX. On the Serum Reactions of Mexican and European Typhus Rickettsia.**]—*Jl. Experim. Med.* 1932. Oct. 1. Vol. 56. No. 4. pp. 455–467.

It has already been shown in Europe that the serum of patients recovered from an attack of typhus fever and also the serum of guineapigs after inoculation with the virus of that disease, will agglutinate an emulsion of Rickettsia from the body fluid of heavily infected lice (Weigl vaccine). The authors have corroborated this observation with the European virus and in addition have employed as antigen an emulsion of Rickettsia obtained from rats infected with the Mexican typhus virus and which had been previously exposed to X-ray irradiation. They found that both these emulsions of Rickettsia were readily agglutinated by the sera of infected guineapigs (this is not the case with Proteus X19) and also by the sera of patients convalescent from the disease whether Mexican or European variety, the homologous strain being if anything agglutinated in higher titre. These results ran in parallel with the Weil-Felix reaction but the Rickettsia appeared to be a more delicate indicator, being agglutinated in higher dilution than the Proteus X19. In addition it was shown that rabbits could be immunized by inoculation with the Rickettsia emulsions and agglutinins were produced in their serums. The serum of the rabbit inoculated with the Weigl vaccine agglutinated the emulsion of Rickettsia

*This case was first described as one of severe typhus (this *Bulletin*, Vol. 29, p. 19), then as typhus with the symptoms of Japanese River fever (*loc. cit.* p. 451) and now as Japanese River fever, *tout court.*

obtained from the rats and the sera of both the rabbits agglutinated Proteus X19 ; *i.e.*, a positive Weil-Felix reaction was produced.

D. H.

Wolff (J. W.). Qualitatieve proteus-X-agglutinatie bij mijtekoorts en tropical typhus. [**Proteus X Agglutination with Mite Fever and Tropical Typhus.**]—*Geneesk. Tijdschr. v. Nederl.-Indië.* 1932. July 5. Vol. 72. No. 14. pp. 896–914. With 1 fig., 4 graphs & 4 figs. on 1 plate. [25 refs.] English summary.

The results are recorded of the Weil-Felix reaction performed in the course of cases of mite fever (tsutsugamushi disease, type Schüffner, Sumatra) and also in cases of tropical typhus. As antigens for the test both living and killed suspensions of the H and O variants of Proteus X19 and Proteus XK strains were used. The suspensions of the H bacilli were preserved in formalin and the O suspensions in alcohol. It was shown in the course of the work that only the O agglutinins are of importance in typhus fever. The results of the agglutination performed with suspensions of the O variants of Proteus X19 and XK may be summarized as follows :—

In the course of mite fever (tsutsugamushi disease) OXK agglutinins are found exclusively ; these agglutinins appear in the 2nd or 3rd week of fever, the peak point being during the 4th week ; examples of agglutinin curves are given in the paper. A few cases of short fever without primary sore which showed some agglutination of OXK were met with ; these were probably cases of so-called scrub typhus. Quite distinct from these were cases of shop or urban typhus (endemic typhus) : the serum of these cases agglutinated OX19 in about the same degree as did the mite fever cases the OXK suspensions. The typhus-like fevers are divided by the author into two serological groups, (1) those which agglutinate OX19 (typhus fever, tabardillo, endemic typhus, shop typhus), (2) those which agglutinate OXK (tsutsugamushi disease, tick bite fever, scrub typhus). It was noted that a higher degree of agglutination was obtained with living suspensions of OX19 than with the killed suspensions, whereas with OXK the opposite was the case.

D. H.

Lima (Carvalho). Bacillo Proteus XL e typho exanthematico de S. Paulo. [**Proteus XL and the S. Paulo Type of Exanthematic Typhus.**]—*Brasil-Medico.* 1933. Jan. 28. Vol. 47. No. 4. pp. 64–66.

This article contains correspondence between the author and Dr. Felix on the S. Paulo type of typhus [see page 391] and gives account of the serological tests performed with strains of Proteus. These were carried out for O (somatic) and H (flagellar) agglutinins to Proteus X2, X19, XK, and a local strain X167. Of fourteen sera examined 11 agglutinated this last at titres between 1 : 200 and 1 : 16,000, and nine of them agglutinated Proteus OX19 at an equal or even higher dilution. Dr. Felix determined Proteus X167 to be " antigenically correspondent to the virus of the endemic typhus of S. Paulo " and he proposes to designate it Proteus XL (the L indicating Lima strain).

H. H. S.

GOMES (Luis Salles). Présence de Rickettsias dans l'endothélium et dans les parois des vaisseaux testiculo-scrotaux de cobayes infectés expérimentalement du typhus exanthématique de Sao Paulo. [**Rickettsia in the Endothelium and Testicular Vessel Walls of Guineapigs infected with S. Paulo Typhus.**]—*C. R. Soc. Biol.* 1932. May 20. Vol. 110. No. 17. pp. 134–136.

The author refers to previous work with the Sao Paulo strain of typhus virus in which Rickettsia was demonstrated in the cells of Descemet's membrane in the eyeball of infected guineapigs and also in the cells in peritoneal membranes after inoculation. [See MONTEIRO, this *Bulletin*, Vol. 29, p. 778.]

The author has now been able to demonstrate Rickettsia in the cells lining the testicular blood vessels in inoculated guineapigs and notes that his results are comparable to those of WOLBACH in Rocky Mountain fever, the organisms being found not in the cells of the serous membrane but in those of the muscular layer of the blood vessels.

No intranuclear forms were ever noted nor were they found in polymorphonuclear cells or in the large mononuclears. Those guineapigs in which Rickettsia were found in the tissues showed high fever and a severe reaction in the testicles. Although excellent preparations were obtained by means of Giemsa stain it was noted that the preparations faded out after 24 hours. This point is being further investigated.

D. H.

CAMINOPETROS (Jean). La réaction scrotale du cobaye provoquée par inoculation des tiques (*Rhipicephalus sanguineus*) infectées avec le virus de la fièvre boutonneuse. [**Scrotal Reaction provoked in the Guineapig by Inoculation of Ticks infected with Eruptive Fever.**]—*C. R. Soc. Biol.* 1932. June 10. Vol. 110. No. 20. pp. 344–346.

The authorities in the South of France have always insisted that eruptive fever of Marseilles is definitely distinct from endemic typhus and have principally based their opinion on two facts, (1) that the Weil-Felix reaction is not positive in eruptive fever, and (2) that guineapigs are not susceptible to the virus. It has, however, been shown by DURAND [this *Bulletin*, Vol. 29, p. 791] that a positive Weil-Felix reaction can be elicited in the disease and now Caminopetros shows that the guineapig reacts to the virus of eruptive fever just as it does to the virus of endemic typhus, *i.e.*, with fever and swelling of the scrotum. Previous attempts had been made to infect guineapigs by injection of the blood of cases of the fever, but it has been shown that the virus is only present in the blood in small quantity (20 cc. of blood is required to carry on infection from man to man).

The author employed in his experiments an emulsion of ticks collected from dogs in an infected area. Intraperitoneal inoculation of male guineapigs was followed after an incubation period of 4 days by fever accompanied by marked scrotal oedema ; the fever lasted from 4 to 6 days and the scrotal reaction 8 days. The skin of the scrotum was infiltrated with small haemorrhages and small necrotic points were noted. The testicles were hard and adherent to the skin and could not be replaced in the abdominal cavity. In animals which were killed thickening and haemorrhagic infiltration of the tunica vaginalis was observed. In short the conditions produced were exactly similar to

those seen on injection of the virus of endemic typhus and known as the Neill-Mooser reaction. Smear preparations of the tunica vaginalis stained by Giemsa showed very numerous Rickettsia-like bodies and proved to be sterile on cultivation.

The ticks used were obtained from the district of Volo where eruptive fever is common ; ticks collected from dogs in Athens, where the fever does not occur, injected into guineapigs did not produce any reaction. *D. H.*

Le Chuiton (F.) & Moureau (M.). Présence d'un virus du typhus murin chez les rats de Bordeaux. Disparition de la périorchite du cobaye au cours des passages. Réceptivité du lapin à ce virus. [**Presence of Virus of Murine Typhus in Bordeaux Rats.**]—*C. R. Soc. Biol.* 1932. Oct. 14. Vol. 111. No. 30. pp. 167–169.

From rats collected in Bordeaux, 5 *decumanus* and 1 *alexandrinus*, an emulsion of the brains was made and inoculated into guineapigs, which gave the usual reaction of fever and swelling of the scrotum. The interesting point was that guineapigs sub-inoculated from these showed fever but no scrotal swelling. A rabbit inoculated from the 3rd passage guineapig (no orchitis) reacted with fever and swelling of the scrotum, and on the 16th day gave a positive Weil-Felix reaction. Brill's disease has not been reported in Bordeaux. *D. H.*

Rochaix (A.), Sédallian (P.) & Couture (E.). Au sujet du rat réservoir de virus d'un typhus à Lyon. [**Rat Reservoir of Typhus Virus at Lyons.**]—*C. R. Soc. Biol.* 1932. Dec. 9. Vol. 111. No. 38. pp. 817–818.

The sera of 65 *M. decumanus* were tested for agglutinins for Proteus X19 ; 9 gave positive reactions. Emulsions were made of the brains of six of the rats which had given positive reactions and inoculated into guineapigs ; after an incubation period of 14 days fever developed but swelling of the scrotum was not noted. The fever lasted 5 or 6 days. *D. H.*

Panayotatou (A.). Les rats réservoirs du typhus exanthématique à Alexandrie. Sérum sanguin de *Mus norvegicus* et *Proteus* X_{19}. [**Rat Reservoirs of Typhus in Alexandria.**]—*C. R. Soc. Biol.* 1932. Nov. 4. Vol. 111. No. 33. pp. 430–431.

In 1929 the author isolated a strain of Proteus X19 from rats in Alexandria and showed that the serum of these rats agglutinated this bacillus in a dilution of 1/800. In 1932 the sera of 50 rats was tested with 3 strains of X19 ; 42 per cent. gave a positive Weil-Felix reaction, the highest titre being 1/1,000. *D. H.*

Panayotatou (A.). Les rats et les puces, réservoirs et vecteurs du typhus exanthématique à Alexandrie. [**Rats and Fleas as Reservoirs and Carriers of Typhus at Alexandria.**]—*C. R. Soc. Biol.* 1932. Nov. 14. Vol. 111. No. 34. pp. 496–498. With 1 fig

Fleas (*X. cheopis*) were collected from rats in Alexandria and an emulsion was made and injected into guineapigs. These animals reacted with fever, marked loss in weight and swelling of the scrotum.

Before inoculation their serum gave a negative Weil-Felix reaction but during convalescence a positive reaction, 1/100, was obtained. Numerous Rickettsia were seen in stained smears from the tunica vaginalis of infected guineapigs. *D. H.*

Lépine (Pierre). Sensibilité du spermophile au typhus exanthématique. [**Susceptibility of the Spermophile to Typhus.**]—*C. R. Acad. Sci.* 1932. July 11. Vol. 195. No. 2. pp. 188–191.

The spermophile inoculated with the virus of endemic typhus (rat) develops fever and general weakness of about four days' duration; there is no testicular or scrotal swelling in the males nor can Rickettsia be demonstrated in smears from organs. The brain emulsion is infective for guineapigs during the incubation period and is still infective on the 31st day 3 weeks after the fever has ceased. The spermophile also reacts to the virus of epidemic typhus with fever which sometimes terminates fatally. Spermophiles in nature do not carry the virus; all attempts to isolate the virus from the normal animals failed.

D. H.

Walker (Ernest Linwood) & Sweeney (Marion A.). **Some Infections simulating Experimental Typhus in the Guinea Pig.**—*Amer. Jl. Trop. Med.* 1932. May. Vol. 12. No. 3. pp. 217–222.

During work on the transmission of typhus virus the authors have noted that organisms may be encountered which give rise to a fever curve and gross pathology resembling but not identical with that of typhus; these reactions can be passed in series and may give rise to error.

The first of these infections encountered was that due to a protozoon of the genus *Toxoplasma*. If injections are made in guineapigs into the skin the protozoon may be readily found at the site of the lesion but not in the blood or spleen, whereas if injections are made intraperitoneally the organism cannot be seen in the blood or tissues. Rabbits on the other hand react readily to the infection and the parasites can be easily seen in their blood. Guineapigs which have reacted to this protozoon are not immune to typhus virus. Checks such as these are necessary from time to time to prevent error.

Another series of guineapigs became infected with a small bacillus of the Salmonella type; this also gave rise to fever and a pathology resembling that of typhus. This bacillus was not agglutinated by typhus serum nor did it produce agglutinins for Proteus X19 in the sera of inoculated rabbits; animals recovered from the infection were not immune to typhus virus. To avoid error it is advisable when transferring the virus from guineapig to guineapig to culture the blood and organs at the same time; if present this small bacillus can be readily isolated.

The authors made many attempts to cultivate Rickettsiae but failed. In view of the close serological association of Proteus X19 with typhus they carried out a very intensive research but in spite of thousands of attempts failed to isolate any strain of Proteus from guineapigs infected with typhus or Rocky Mountain fever virus. They succeeded in infecting guineapigs with small doses of Proteus X19 and produced a fever curve and pathology resembling that of typhus but animals recovered from Proteus infection were not immune to typhus virus.

D. H.

DYER (R. E.), WORKMAN (W. G.), RUMREICH (A.) & BADGER (L. F.). **The Preparation of a Vaccine from Fleas infected with Endemic Typhus.**—*Public Health Rep.* 1932. June 17. Vol. 47. No. 25. pp. 1329–1331.

The fleas utilized in these experiments were of the species *Xenopsylla cheopis*. After feeding on infected rats they were collected and emulsified in salt solution. The emulsion was phenolized and the supernatant fluid in doses of 1 cc. was injected into 24 guineapigs, 12 of which received a second dose of 0·5 cc. one week later. Out of 20 tested later 16 were found to be non-immune. A stronger vaccine was prepared and 44 guineapigs received 1 cc. each ; 6 out of 8 were non-immune after test 3 weeks later, but of the remaining 16, 8 were immune when tested after another 3 months. In the first experiment no evidence of protection was shown but in the 2nd experiment there was definite evidence. It is proposed to try again with a more potent vaccine, that is employing fleas containing a greater amount of virus, 1/10,000 to 1/100,000 of a flea affording an infective dose, whereas in the above experiments 1/5 flea was required. *D. H.*

NICOLLE (Charles) & SPARROW (Hélène). Application au cobaye et à l'homme de la méthode de vaccination contre le typhus exanthématique par emploi d'intestins phéniqués de poux (méthode de Weigl). [**Weigl's Vaccination Method applied to Guineapig and Man.**]—*Arch. Inst. Pasteur de Tunis.* 1932. July. Vol. 21. No. 1. pp. 25–31.

Technique of preparation of Weigl's vaccine.—Clean lice are bred in the laboratory, a few of these are inoculated by the anal route by means of a special glass pipette. The virus is obtained either from the blood of a case of acute typhus or from the blood or organs of an infected guineapig. The lice become infected and Rickettsia multiply rapidly in the cells lining the intestine : these cells eventually rupture and the Rickettsia are discharged in enormous numbers into the intestine, the lice eventually (in 9 or 10 days) succumbing to the infection. Fresh lice are inoculated by the same method from these lice, an expert worker inoculates 1,000 lice in a day It is calculated that a single louse may contain from 10 to 100 million Rickettsia. The infected lice are dissected and the intestines removed in a sterile manner and ground up in a normal saline and a small quantity, 0·5 per cent., of carbolic added to the emulsion : this forms the vaccine and the dose is approximately 150 intestines per man, divided into 3 doses.

WEIGL has shown that guineapigs and monkeys can be protected from infection by means of this vaccine. Nicolle repeated this work and found good protection in 5 guineapigs and one monkey ; none of the protected animals reacted to test doses whereas all the controls did so. Four children were inoculated each with 3 doses of vaccine and their sera gave a positive Weil-Felix reaction after the third dose. These children were given a test dose but showed no reaction. Nicolle recommends that all workers with typhus virus should be protected by vaccination. *D. H.*

GROUP OF TYPHUS-LIKE DISEASES.

[See Major-General D. HARVEY's article on "Typhus and Typhus-like Diseases," pp. 343–349 above.]

Disease	Distribution	Reservoir	Vector	Virus	Clinical Symptoms, Fever Rash, Nerve Symptoms, etc.	Neill-Mooser Reaction in Guineapigs	Typhus Nodules	Weil-Felix Reaction B. proteus. X	
								Type X 19	Type X.K.
Epidemic Typhus	Worldwide ...	Man ...	Louse ...	*R. prowazeki*	Present	Only very occasionally	+ + +	+ + +	—
Endemic Typhus Brill's Disease	Worldwide ...	Rat ...	Flea *X. cheopis*	*R. prowazeki*	Present	Constant	+ +	+ + +	—
Rocky Mountain Fever	N. America West and East	Rabbit, Squirrel, etc.	Tick *D. venustus* *D. variabilis*	*R. rickettsii*	Present	Constant + gangrene	+ +	+ ±	+ ?
Japanese River Fever	Japan Sumatra Malaya Cochin China	Field Mice	Mite *T. akumushi*	*R. orientalis*	Present + primary ulcer	Present	+ +	—	+ ±
Fièvre boutonneuse	Mediterranean region	Dog	Tick *R. sanguineus*	*R. conori*	Present + primary ulcer	Present	+ +	+ ±	—
African Tick Typhus	S. Africa ...	Dog ? ...	Tick *R. sanguineus*	Rickettsia present	Present + primary ulcer	Present	+ +	+ ±	+ + ±
Tropical Typhus	Malaya Sumatra Australia Kenya								
"W" Form	... ...	Rat ...	Flea *X. cheopis*	*R. prowazeki*	Present	Present	+ +	+ + +	—
"K" Form	... ...	?	?	*R. prowazeki*	Present	Present	+ +	—	+ + +

With a subject which is being advanced daily on one or other of its fronts, a table such as this can have only a relative value. Other tables differing in detail exist, *e.g.*, *Jl. Trop. Med. & Hyg.*, 1930, Vol. 33, facing p. 302 (JEWELL & CORMACK); *Jl. of Hygiene*, 1931, Vol. 31, p. 244 (FELIX & RHODES); *Ztschr. f. Immunitätsf. u. Experim. Therap.*, 1932, Vol. 74, p. 360 (KRAUS); *Annals of Internal Med.*, 1932, Oct., Vol. 6, No. 4, pp. 550–553 (TOOMEY); and *Boll. Ist. Sieroterap. Milan.*, 1933, Vol. 12, pp. 244–5 (REITANO).

S. Paulo typhus is omitted because when the article was received knowledge of this form was uncertain (see FIALHO, this *Bulletin* p. 391). More recent work suggests the transfer of Kenya typhus to the African tick typhus group.

DENGUE.

McSwan (D. M.). **The Dengue-like Fevers.**—*Malayan Med. Jl.* 1932. June. Vol. 7. No. 2. pp. 49–52. With 1 chart.

The author divides the dengue-like fevers into two groups, (*a*) 3-day or 3 to 5-day fever, (*b*) 7-day or 7 to 10-day fever. These fevers are accompanied at some period of the febrile or post-febrile state by a variety of exanthemata, which may range from a slight reddening of the skin of the neck to a definite macular erythema or morbilliform eruption. Three types of the 3-day fever are noted: (1) sandfly fever type with injected conjunctivae, (2) similar but with rash and diarrhoea in addition, (3) an abortive dengue-like fever with rash and pains in the joints. Two types of the 7-day fever are met with: (1) fever continuous for seven days with intense joint pains and morbilliform rash, (2) similar to (1) but without the joint pains. *D. Harvey.*

Gauguet. Sur quelques cas de dengue observés à la marine à Dakar. [**Dengue in the French Navy at Dakar.**]—*Arch. Méd. et Pharm. Nav.* 1932. July–Aug.–Sept. Vol. 122. No. 3. pp. 263–269.

In view of the occurrence of several causes of yellow fever in stations visited by the French West African fleet the author was on the lookout for suspicious cases. All cases of fever were treated under nets or preferably in screened wards; the blood was examined for protozoa and the amount of albumen in the urine carefully estimated. Several cases of dengue were detected, and one at least of these showed an amount of albumen in the urine which, apart from other symptoms, might have been considered diagnostic of yellow fever. All the patients recovered. *D. H.*

Hoffmann (J. M.), Mertens (W. K.) & Snijders (E. P.). De overbrenging van de Javaansche "endemische dengue" naar Amsterdam. [**Javanese "Endemic Dengue" transferred to Amsterdam.**]—*Geneesk. Tijdschr. v. Nederl.-Indië.* 1932. Aug. 30. Vol. 72. No. 18. pp. 1195–1199. With 5 figs. on 2 plates.

Dried serum from a case of endemic dengue of Java produced a typical case of the disease at Amsterdam, after being kept for 285 days. The serum of the patient at Amsterdam injected into another individual gave rise to a similar disease. Both these cases were so like the previously studied cases of spontaneous and experimental dengue of Sumatra that it does not appear justifiable to differentiate between Javanese and Sumatran dengue. Neither is there sufficient reason to consider the so-called "van der Scheer's fever" as a separate disease (see also this *Bulletin*, Vol. 28, p. 621). *W. J. Bais.*

Findlay (G. M.). **The Relation between Dengue and Rift Valley Fever.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1932. Aug. 11. Vol. 26. No. 2. pp. 157–160.

Findlay, working with a dengue virus obtained from Amsterdam, found that monkeys which had been infected with this virus and recovered were not immune to subsequent inoculation of the virus of Rift Valley fever. On the other hand monkeys which had recovered from Rift Valley fever reacted later to dengue virus as shown by leucopenia and infectivity of the blood for a volunteer. *D. H.*

LORANDO (N. J.). Etude critique sur l'épidémie de l'île de Syra. Dengue et spirochétose. [**The Syra Epidemic : Dengue and Spirochaetosis.**]—*Bull. Soc. Path. Exot.* 1932. June 8. Vol. 25. No. 6. pp. 552–558. [12 refs.]

A sudden outbreak of fever with jaundice occurred in the island of Syra in the Greek Archipelago ; 25 cases in all were reported, 12 with severe, 13 with light jaundice ; 3 patients died. Bilious vomiting was a prominent symptom in the severe cases, a symptom that has not so far been reported in dengue, which had been suggested as a possible diagnosis. The urine contained a trace of albumen from the commencement of the fever and later a larger amount with bile salts and bile pigment. Complete anuria was noted in one of the fatal cases. Bile pigments were absent from the stools. A morbilliform rash was noted, becoming haemorrhagic in some cases. A diagnosis of spirochaetal jaundice was made, and confirmed by successful inoculation of a guineapig. Dengue was present in the island at the same period. The author notes that Dr. FLONQUIN described cases of spirochaetal jaundice in Smyrna so long ago as 1835 under the name of " icteric typhus," or " yellow fever of Smyrna." *D. H.*

PURCELL (Frederick W.). **Notes of a Case of Fever in Some Respects resembling Mild Dengue Fever.**—*West African Med. Jl.* 1932. July. Vol. 6. No. 1. p. 6. With 1 chart.

A case of fever seen in Nigeria with rose rash on abdomen, chest and arms, not on extremities. No bone pains but pains in muscles and post orbital headache. Four days fever, one day intermission and secondary rise on 6th day. *D. H.*

CULLEN (J. P.). Dengue Fever.—*Jl. Trop. Med. & Hyg.* 1932. Oct. 1. Vol. 35. No. 19. pp. 289–290. With 3 charts.

WATSON (Malcolm). A Case of Dengue Fever with Hyperpyrexia.—*Malayan Med. Jl.* 1932. Sept. Vol. 7. No. 3. p. 92.

REVIEWS AND NOTICES.

OLMER (D.). [Professeur de clinique médicale à la Faculté de Médecine de Marseille] & OLMER (Jean) [Chef de clinique médicale à la Faculté de Médecine de Marseille]. **Fièvre boutonneuse. Fièvre exanthématique du littoral Méditerranéen.** [Fièvre Boutonneuse: Eruptive Fever of the Mediterranean Coast.]—106 pp. With 10 figs. (1 coloured). 1933. Paris, VI: Masson et Cie, 120 Boulevard Saint-Germain. [17 fr.]

This little book gives a succinct account of the interesting disease which the authors have been studying in Marseilles for the last ten years. In 1925, one of them (D. Olmer) first drew attention to its occurrence in the suburbs of the town and, later, he gave it the name of *Fièvre Exanthématique*. Subsequently, it was shown to be identical with an eruptive fever described in 1910 by CONOR and BRUCH in Tunis, under the name *Fièvre Boutonneuse* (*bouton*=pimple), and it was decided at the first International Congress of Hygiene at Marseilles, as suggested by Professor NICOLLE, to retain "*fièvre boutonneuse*" as the name of the fever in question, and to reserve the term "*fièvres exanthématiques*" for the whole group of those eruptive fevers of which typhus exanthematicus is the type. *Fièvre boutonneuse* is itself a member of this group; indeed, its close resemblance to typhus was the cause of much anxiety and grave apprehension when it appeared in Marseilles.

It was regarded, at first, as a rare disease of limited distribution, but now—in addition to Marseilles and its environs, where it has become more common—it has been recognized throughout the Midi (Nice, Cannes, La Ciotat, the Var, Nimes, Montpellier, etc.), along the Mediterranean coast (France, Spain, Morocco, Algiers, Tunis, Tripoli, Egypt, Greece, Syria) and in Portugal, Rumania and the Sudan. The authors look upon it as a new disease in France, and they think that it was probably imported from Africa.

Its nosological position has been the subject of much debate. The Weil-Felix reaction is often positive in dilutions of 1 in 100 to 1 in 1,000, but it is inconstant and does not occur until early convalescence. It is evident from this that the disease is related to typhus, but that it is not identical with it. Sections of the skin show a thickening of the endothelium of the small vessels and precapillaries, with a surrounding perivascular infiltration, such as is seen in other diseases of the typhus group. Clinically, it is milder than typhus and though restlessness and delirium may occur, they rarely pass into stupor; it almost invariably terminates in recovery except in the aged, and the case mortality is only 2 per cent. The temperature charts given in this book show that though the duration of the fever is the same as in typhus, it is not maintained at a high level with a sudden fall at the end, but declines by more gradual lysis. The rash resembles that of typhus, but its distribution is rather different; the face, the palms and soles are spared in typhus, but in *fièvre boutonneuse* they are affected, as they are in Rocky Mountain fever and the tsutsugamushi disease. A small primary lesion, resembling the characteristic lesion of the latter disease, is often present; it is a small black scab, surrounded by a red areola, and occasionally the nearest lymphatic glands are enlarged. This black spot was first described by PIÉRI, BRUGEAS and BOINET in 1925, when they gave it the name of the *tache noire*.

The *fièvre boutonneuse* differs from typhus in its epidemiology and its etiology even more than in its symptomology. It occurs quite apart from infestation with lice; it is a disease of the summer instead of the winter; it occurs in limited areas; it does not spread from person to person and there is no necessity to isolate the sick; it attacks the clean and well-to-do as often as it attacks others; farmers and gardeners are frequent victims. BURNET and D. Olmer, in 1928, put an end to the discussions as to the

identity of *fièvre boutonneuse* with typhus, by infecting monkeys with these two diseases and showing that there was no cross immunity between them.

The blood is infective during the course of the fever, and the disease can be transmitted from the sick to the healthy by its inoculation; but the authors and their colleagues have shown that lice fed upon patients, or infected monkeys, do not convey the disease. They had already drawn attention to the history of tick-bites and of close association with dogs given by many of their patients, when, in 1930, DURAND and CONSEIL succeeded in infecting volunteers by inoculating them with an emulsion of ticks (*Rhipicephalus sanguineus*) collected from a dog belonging to a patient who was suffering from the disease. Similar results were obtained by BRUMPT, and by JOYEUX and PIÉRI, with ticks collected from patients' houses. These observers showed that the infection was transmitted from the adult tick to its eggs, and also from the nymph to the adult, as in Rocky Mountain fever.

The authors look upon the *fièvre boutonneuse* as being more nearly related to Rocky Mountain fever and the tsutsugamushi disease than to typhus, and as being quite distinct from the rat-borne, typhus-like fever described by MARCANDIER and PLAZY (with a regularly positive Weil-Felix reaction) in the harbour of Toulon (a fever which appears to be a mild form of non-louse-borne typhus, akin to Brill's disease).

W. Fletcher.

SOCIÉTÉ DES NATIONS. **Programme des cours de malariologie institués par l'organisation d'hygiène de la Société des Nations. I. Cours théoriques avec travaux pratiques donnés à Hambourg, Paris et Rome. II. Stages d'application dans des régions malariques.** [Program of Courses in Malariology organized by League of Nations.] 1933. C.H./Malaria/190. 24 pp.

The Malaria Commission of the League of Nations noted in the course of its visits to malarious parts of Europe that the number of doctors trained in the epidemiology of the disease and the application of anti-malarial measures was insufficient. It has therefore organized courses of malariology both theoretical and practical in Paris, Hamburg and Rome. In London the usual course of parasitology can be taken at the School of Hygiene with modifications. The three courses are here described. The second part of the plan consists in two separate months spent in practical work in a malarious country and here Spain and Yugo-Slavia (Skoplje) have been pressed into service. The conditions of entry to these courses, dates, fees, methods of application, are here set out. *A. G. B.*

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